Appendix A

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ORIGINAL REPORT

Gefitinib in Combination With Paclitaxel and Carboplatin in Advanced Non–Small-Cell Lung Cancer: A Phase III Trial—INTACT 2

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose

Preclinical studies indicate that gefitinib (Iressa, ZD1839; AstraZeneca, Wilmington, DE), an orally active epidermal growth factor receptor tyrosine kinase inhibitor, may enhance antitumor efficacy of cytotoxics, and combination with paclitaxel and carboplatin had acceptable tolerability in a phase I trial. Gefitinib monotherapy demonstrated unparalleled antitumor activity for a biologic agent, with less toxicity than docetaxel, in phase II trials in refractory, advanced non–small-cell lung cancer (NSCLC). This phase III, randomized, placebo-controlled, double-blind trial evaluated gefitinib plus paclitaxel and carboplatin in chemotherapy-naive patients with advanced NSCLC.

Patients and Methods

Patients received paclitaxel 225 mg/m^2 and carboplatin area under concentration/time curve of 6 mg/min/mL (day 1 every 3 weeks) plus gefitinib 500 mg/d, gefitinib 250 mg/d, or placebo. After a maximum of six cycles, daily gefitinib or placebo continued until disease progression. End points included overall survival, time to progression (TTP), response rate (RR), and safety evaluation.

Results

A total of 1,037 patients were recruited. Baseline demographic characteristics were well balanced. There was no difference in overall survival (median, 8.7, 9.8, and 9.9 months for gefitinib 500 mg/d, 250 mg/d, and placebo, respectively; $P = .64$), TTP, or RR between arms. Expected dose-related diarrhea and skin toxicity were observed in gefitinib-treated patients, with no new significant/unexpected safety findings from combination with chemotherapy. Subset analysis of patients with adenocarcinoma who received ≥ 90 days' chemotherapy demonstrated statistically significant prolonged survival, suggesting a gefitinib maintenance effect.

Conclusion

Gefitinib showed no added benefit in survival, TTP, or RR compared with standard chemotherapy alone. This large, placebo-controlled trial confirmed the favorable gefitinib safety profile observed in phase I and II monotherapy trials.

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INTRODUCTION

Lung cancer is the most common cause of cancer death worldwide [1]. Current first-line chemotherapy options for patients with advanced non–small-cell lung cancer (NSCLC), such as the combination of a platinum-based agent with paclitaxel, gemcitabine, vinorelbine, or docetaxel, have substantial toxicity and seem to have reached a plateau in terms of efficacy. A randomized study by the Southwest Oncology Group showed that paclitaxel with carboplatin has similar efficacy to vinorelbine with cisplatin (median survival, 8 months for both regimens; 1-year survival, 38% and 36%, respectively) [2]. More recently, a study by the Eastern Cooperative Oncology Group found that four different platinum-based regimens had similar efficacies [3]. Clearly, improve-

ment on these existing treatments for advanced NSCLC is needed, requiring the development of new agents with a different mechanism of action and an improved safety profile compared with chemotherapy.

The orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib (Iressa, ZD1839; AstraZeneca, Wilmington, DE) blocks signal transduction pathways implicated in the proliferation and survival of cancer cells [4]. Four phase I studies have shown that gefitinib is generally well tolerated, with evidence of antitumor activity in a range of tumors including NSCLC [5-8]. Observations and pharmacokinetic data from these trials identified two doses for further study: gefitinib 250 mg/d is higher than the lowest dose at which clinical response was seen, and 500 mg/d is the highest dose level to be tolerated long-term by most patients. Two large phase II gefitinib monotherapy studies (Iressa Dose Evaluation in Advanced Lung Cancer [IDEAL] 1 and 2) in patients with pretreated advanced NSCLC further confirmed that this agent was generally well tolerated and produced durable, clinically significant antitumor activity (response rates for gefitinib 250 mg/d were 18.4% and 11.8% for IDEAL 1 and 2, respectively), with improvement in disease-related symptoms observed in approximately 40% of symptomatic patients [9-11]. These response rates for patients receiving second-line and higher therapy were encouraging, particularly when considered in the context of the retrospective analysis by Massarelli et al [12], in which the response rate declined with each line of therapy (second line, 16.3%; third line, 2.3%). The most frequent drug-related adverse events observed in these two trials were skin rash and diarrhea, which were generally mild (grade 1 and 2). The results of randomized studies are awaited.

There is a strong rationale for combining gefitinib with standard chemotherapy agents. In preclinical studies, gefitinib enhanced the efficacy of cytotoxic agents against a range of human tumor xenografts, including lung cancer, regardless of EGFR expression [13,14]. A small phase I study of 24 patients with chemotherapy-naïve, advanced NSCLC showed that gefitinib in combination with paclitaxel and carboplatin was well tolerated, with no clinically significant pharmacokinetic drug-drug interactions [15]. Together, these preclinical data, data from gefitinib single-agent trials, and the favorable tolerability data from the phase I trial of this combination supported phase III investigation.

The Iressa NSCLC Trial Assessing Combination Treatment (INTACT) 2 was a randomized, placebo-controlled trial of paclitaxel and carboplatin with or without gefitinib in chemotherapy-naive patients with advanced NSCLC. This global multicenter study was conducted mainly (80%) in the United States; INTACT 1, a parallel global trial that evaluated the combination of gefitinib with gemcitabine and cisplatin, was conducted mainly in Europe. The results of INTACT 1 are reported elsewhere [16]. The primary objective of INTACT 2 was to determine overall survival, and the secondary end point was time to progression. Additional end points included objective response rate, disease-related symptom and quality-of-life outcomes, and adverse-event profiling.

PATIENTS AND METHODS

Eligibility Criteria

Patients were assessed by physical examination and history to ensure that eligibility criteria were met. Entry criteria included histologically confirmed NSCLC (cytologic specimens obtained by brushing, washing, or needle aspiration of a defined lesion were acceptable), unresectable stage III or IV disease, no prior chemotherapy, age ≥ 18 years, and performance status 0 to 2. Exclusion criteria included the presence of mixed NSCLC or small-cell lung cancer, brain metastases that were newly diagnosed or had not been treated with surgery or radiation, previously treated CNS metastases or spinal-cord compression in the absence of clinically stable disease, less than 2 weeks since radiotherapy, unresolved toxicity from prior radiotherapy or incomplete healing from

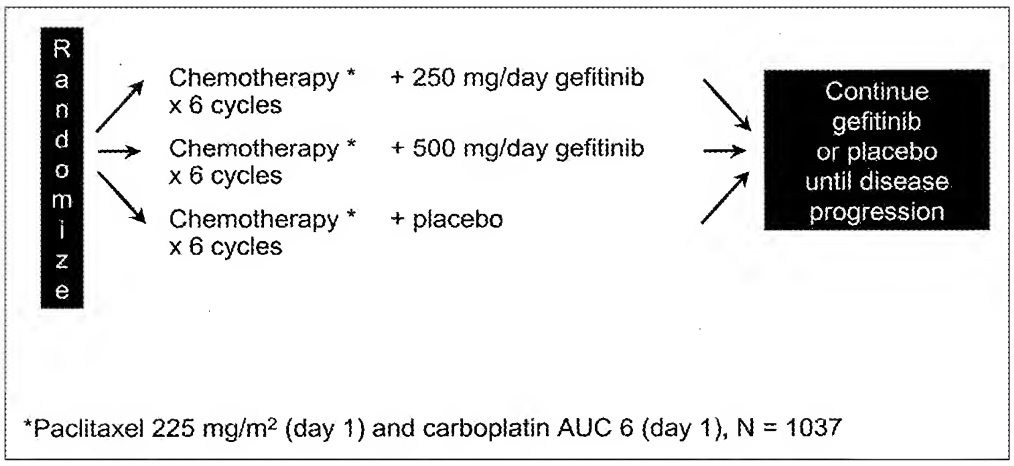

Fig 1. INTACT 2 trial schema. AUC, area under concentration-time curve.

Table 1. Patient Characteristics

	Gefitinib 500 mg/d (n = 347)	Gefitinib 250 mg/d (n = 345)	Placebo (n = 345)
Sex, %			
Female	40.1	42.3	38.6
Male	59.9	57.7	61.4
Age, years			
Median	62	61	63
Range	26–82	27–86	31–85
Disease stage, %*			
IIIa	2.6	2.3	3.8
IIIb	15.3	16.2	17.1
Without pleural effusion	3.5	3.2	5.2
With pleural effusion	11.8	13.0	11.9
IV	81.8	81.2	78.3
WHO performance status, %*			
0	34.6	33.0	38.6
1	51.9	56.5	51.9
2	13.3	10.4	9.3
Weight loss in previous 6 months, %*			
≤ 5%	59.1	62.6	60.9
> 5%	39.5	37.1	38.3
Disease measurability, %*			
Measurable	93.9	91.3	88.4
Nonmeasurable	5.8	7.8	11.0
Histology, %*			
Squamous	16.7	20.3	19.4
Adenocarcinoma	57.9	55.7	51.9
Adenosquamous	2.9	2.3	1.7
Bronchoalveolar	2.9	2.9	3.2
Unspecified NSCLC	11.5	9.6	11.3
Large cell	7.2	8.7	11.0
Race, %			
White	88.5	90.4	91.9
Black	7.5	4.1	5.2
Other	4.0	5.5	2.9

Abbreviation: NSCLC, non–small-cell lung cancer.
*Information was not available for all patients.

surgery, evidence of severe systemic disease, greater than trace blood or protein on repeat urinalysis, absolute neutrophil count less than 2,000/μL, WBCs less than 4,000/μL, platelets less than 100,000/μL, serum bilirubin greater than 1.25 times the upper limit of reference range (ULRR); ALT or AST greater than 2.5 times ULRR (> five times ULRR in the presence of liver metastases), serum creatinine greater than 1.5 times ULRR, pregnancy or breast-feeding, and hypersensitivity to mannitol, corticosteroids, H_2-antagonists, antihistamines, or agents formulated with polyoxyethylated castor oil.

All patients gave written informed consent and approval was obtained from the ethics committee at each trial center. The study followed the Declaration of Helsinki [17] and good clinical practice guidelines.

Trial Design

All patients received chemotherapy (intravenous paclitaxel 225 mg/m^2 over 3 hours on day 1 of a 3-week cycle immediately followed by intravenous carboplatin area under concentration/time curve [18] of 6 mg/min/mL over 15 to 30 minutes on day 1) and were randomized to receive either oral gefitinib at 250 or 500 mg/d or daily oral placebo (Fig 1). Chemotherapy was continued for six cycles in the absence of disease progression. Thereafter, patients were maintained on gefitinib or placebo until disease progression or drug intolerance.

Before randomization, patients were stratified according to weight loss in the previous 6 months (≤ 5% *v* > 5%), disease stage (III *v* IV), performance status (0 or 1 *v* 2), and the presence of measurable disease (yes *v* no).

Statistical Analysis

The trial was governed by a steering committee of INTACT principal investigators. The ongoing safety review and interim analyses were conducted by an Independent Data Monitoring Committee. The first interim analysis was for safety, to rule out a detrimental survival effect for gefitinib early in the trial.

Gefitinib was compared with placebo on an intent-to-treat basis with respect to overall survival. The study was designed to have 90% power for a two-sided overall significance level test of the hypothesis that gefitinib increases survival relative to placebo, given a hazard ratio of 1.33. Assuming a 1-year survival rate of 30% in the placebo arm, in line with the data available at the time of

protocol writing, this hazard ratio equates to an increase in median survival of 2.3 months for both gefitinib arms. The final analysis of overall survival was planned to include 750 events. Based on the study design assumptions, 1,029 patients were required.

At the final analysis, an adaptive survival analysis procedure was used that tested either for a positive or negative gefitinib dose-response relationship, based on prospective criteria applied to the observed data. A survival trend test (global ordered log-rank [GOLrank] test), in which the hypothesis was no effect versus the specific ordering of placebo, gefitinib 250 mg/d, and gefitinib 500 mg/d, was used for a positive dose-response, whereas pairwise log-rank tests would be used for a mixed dose-response [19]. To preserve an overall two-sided 5% significance level, and to account for the use of a survival trend test at the second interim analysis, simulations with the adaptive procedure were used to calculate a nominal significance level of 4.4% for the final analysis. According to prospective criteria for the adaptive procedure, the final analysis used a survival trend test to compare survival between the treatment arms.

A posthoc multivariate analysis with eight prespecified prognostic factors at trial entry (disease stage III v IV; performance status 0 or 1 v 2; weight loss in prior 6 months $\leq$ 5% $v >$ 5%; sex; histology; presence or absence of metastases to bone, liver, or brain) was performed to assess which variables were predictive of improved survival.

In a posthoc subgroup analysis, stratification and prognostic factors (disease stage III v IV; performance status 0 or 1 v 2; weight loss in prior 6 months $\leq$ 5% $v >$ 5%; presence or absence of metastases to bone, liver, or brain) and subgroups of sex, time on chemotherapy, and histology were analyzed in a univariate model. An unadjusted Cox proportional hazard test was applied to the overall survival data for each subgroup to estimate the hazard ratio and 95% CI for the treatment comparisons of gefitinib 250 or 500 mg/d versus placebo.

Assessments

Overall survival and time to progression were assessed from the date of randomization to the date of death (any cause) and the date of objective disease progression (death was considered a progression event in patients who died before disease progression), respectively. Patients without documented death or objective progression at the time of the final analysis were censored at the date last known to be alive or their last objective tumor assessment, respectively.

Tumor response was evaluated according to Response Evaluation Criteria In Solid Tumors, the revised version of the International Union Against Cancer/WHO criteria [20].

During the trial, and for 30 days after the last dose of gefitinib or placebo, patients were monitored for adverse events, graded according to the National Cancer Institute Common Toxicity Criteria (CTC) version 2.0. Hematology and biochemistry assessments were performed $\leq$ 7 days before the date of randomization and at each clinic visit. Analysis of other end points, such as symptom improvement rate, quality of life, and correlation of EGFR with survival, is ongoing and will be reported separately.

RESULTS

Patients

In total, 1,037 patients were recruited between May 2000 and April 2001, approximately 80% of whom were in the United States. The baseline characteristics of the patients were similar in each of the three treatment groups (Table 1). Most patients (approximately 80%) had metastatic stage IV disease, and more than 50% of patients in each group had adenocarcinoma. Approximately 20% of patients in each of the treatment groups are confirmed to have continued receiving chemotherapy after withdrawal from the study.

Efficacy

At each interim analysis, the Independent Data Monitoring Committee made recommendations to continue the trial. A total of 725 events (246, 232, and 247 events for gefitinib 500 mg/d, gefitinib 250 mg/d, and placebo, respectively) were observed for survival and 637 events (178, 215, and 244 events, respectively) for time to progression, with a minimum follow-up of 12 months for survival and 6 months for all other end points.

At the final analysis, neither dose of gefitinib improved overall survival when added to paclitaxel and carboplatin compared with paclitaxel and carboplatin plus placebo (GOLrank $P = .6385$). Median survival was 8.7, 9.8, and 9.9 months in the gefitinib 500 mg/d, gefitinib 250 mg/d, and placebo arms, respectively (Fig 2A). The 1-year survival

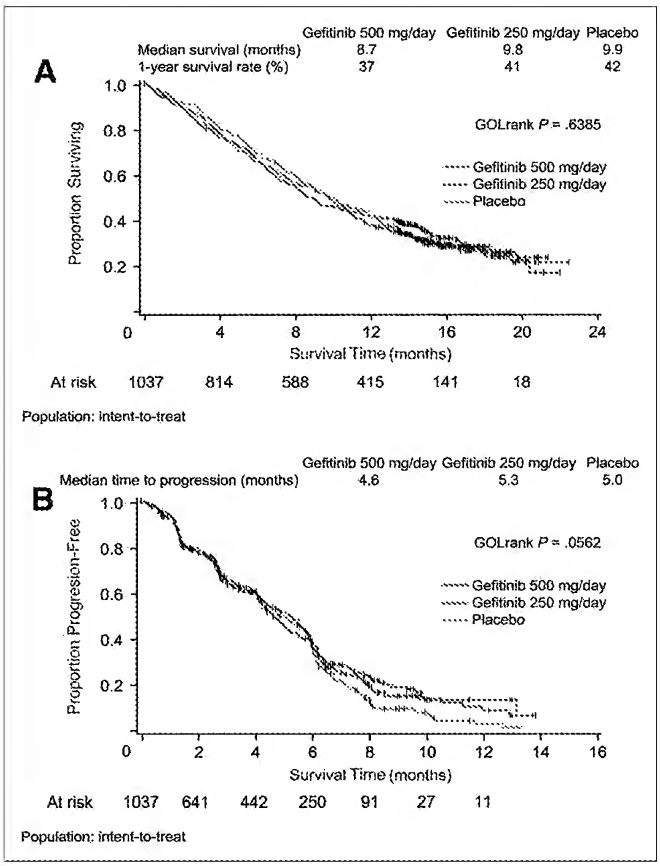

Fig 2. Kaplan-Meier estimates of (A) overall survival and (B) time to progression. GOLrank, global ordered log-rank test.

Table 2. Unadjusted Cox Proportional Hazard Model: Survival by Subgroup (ITT population)

Factor	Placebo *v* Gefitinib 250 mg/d			Placebo *v* Gefitinib 500 mg/d		
	Hazard Ratio*	95% CI	*P*	Hazard Ratio*	95% CI	*P*
Sex						
Male	1.074	0.858 to 1.345	.531	1.112	0.891 to 1.388	.349
Female	0.945	0.700 to 1.277	.714	0.761	0.567 to 1.023	.070
Disease stage						
III	0.986	0.651 to 1.492	.947	1.312	0.845 to 2.036	.226
IV	1.060	0.868 to 1.294	.571	0.917	0.754 to 1.114	.381
Performance status						
0 or 1	1.047	0.864 to 1.269	.641	1.003	0.827 to 1.215	.980
2	0.972	0.587 to 1.610	.911	0.903	0.567 to 1.439	.668
Weight loss in the 6 months prior to entry						
≤ 5%	1.034	0.814 to 1.314	.786	0.974	0.767 to 1.237	.829
> 5%	1.012	0.771 to 1.328	.933	0.951	0.728 to 1.243	.714
Histology type						
Adenocarcinoma, including bronchoalveolar carcinoma	1.156	0.905 to 1.476	.247	1.030	0.812 to 1.306	.808
Other	0.919	0.642 to 1.315	.642	0.738	0.523 to 1.042	.084
Metastases						
Bone	0.835	0.595 to 1.171	.296	0.946	0.685 to 1.307	.737
Liver	1.028	0.703 to 1.503	.887	0.899	0.617 to 1.311	.580
Brain	1.727	0.727 to 4.104	.216	0.673	0.335 to 1.352	.266

Abbreviation: ITT, intention to treat.
*A hazard ratio greater than 1 indicates that patients who received 250 or 500 mg/d of gefitinib live longer than those given placebo. A hazard ratio less than 1 indicates that patients who received placebo live longer than those given 250 or 500 mg/d of gefitinib.

rates were 37%, 41%, and 42%, respectively. Similarly, there was no statistically significant difference between the three groups in median time to progression (4.6, 5.3, and 5.0 months, respectively; GOLrank $P = .0562$; Fig 2B).

In the posthoc multivariate analysis, performance status of 2, weight loss, and bone and liver metastases were significant ($P < .05$) predictors of worse survival outcome. Survival differences were also seen for sex and brain metastases. For the posthoc univariate analysis, generally similar patterns were observed in each of the subgroup analyses, showing no overall difference between treatment groups ($P > .05$, not significant; Table 2). There was no survival advantage in any of the subgroups when gefitinib at any dose was added to chemotherapy. However, there was a trend toward improved survival in the subgroup of patients with adenocarcinoma who had received chemotherapy for ≥ 90 days (patients would have received at least the median number of chemotherapy cycles) in the gefitinib 250 mg/d arm ($P = .05$; Fig 3), suggesting a possible effect of gefitinib monotherapy as maintenance therapy. Although this trend continued for other subgroups (Table 3), the numbers were too small to yield statistical significance.

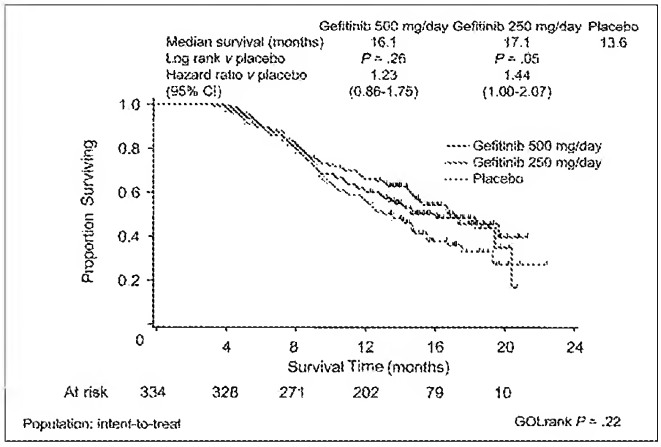

Fig 3. Subset analysis of patients with adenocarcinoma who received ≥ 90 days of chemotherapy. GOLrank, global ordered log-rank test.

Complete responses were rare, observed in 0.6%, 2.6%, and 1.2% of patients in the gefitinib 500 mg/d, gefitinib 250 mg/d, and placebo arms, respectively, and overall response rates were 30.0%, 30.4%, and 28.7%, respectively, demonstrating no statistically significant efficacy difference between treatment arms.

Duration of Therapy, Dose Adherence, and Dose-Intensity

Patients receiving gefitinib 250 mg/d or placebo had a longer duration of therapy than those receiving gefitinib 500 mg/d (Table 4). Similarly, the number of gefitinib dose interruptions and reductions was highest in the gefitinib 500 mg/d arm and similar in the gefitinib 250 mg/d and placebo arms. There was a high overall adherence to gefitinib, and the median dose-intensity for both paclitaxel and carboplatin was similar in all treatment arms (Table 4).

Table 3. Landmark Analyses

Chemotherapy	No. of Patients	Median Survival (months)		
		Gefitinib 500 mg/d	Gefitinib 250 mg/d	Placebo
≥ 90 days	599	14.1	14.9	13.0
≥ 90 days + adenocarcinoma	334	16.1	17.1	13.6
≥ 90 days + stage IV disease	458	12.0	15.1	12.6
≥ 90 days + adenocarcinoma + stage IV disease	260	13.7	19.7	12.5

Safety and Tolerability

Most adverse events occurred during combination treatment and many were attributed to chemotherapy. The safety profile of gefitinib from the monotherapy phase of the trial was similar to that seen in the phase II program. The most common adverse events were gastrointestinal, skin-related, and hematologic in nature. The incidence of acne and rash by grade is shown in Table 5; most of these events were mild (grade 1 or 2). Hematologic adverse events occurred with similar incidence in all three treatment groups, consistent with the toxicity profile of chemotherapy. Gefitinib did not seem to exacerbate these toxicities. Interstitial lung disease (ILD)–type events were experienced by 1.5%, 2.1% and 0.9% of patients in the gefitinib 500 mg/d, gefitinib 250 mg/d, and placebo arms, respectively, and the incidence of dyspnea and other pulmonary adverse events such as cough and pneumonia were generally similar across treatment arms (Table 6). For those adverse events considered to be drug-related (possibly related to gefitinib or placebo), there was a gefitinib dose-response relationship for skin and gastrointestinal events (Table 7). The most frequent grade 3 or 4 drug-related adverse events were diarrhea and rash, which occurred at a higher incidence in the gefitinib 500 mg/d arm than in the gefitinib 250 mg/d or placebo arms (Table 7). Statistical analysis of prespecified adverse events during the chemotherapy phase revealed no difference between treatment arms except for diarrhea ($P <$ .0001 for gefitinib 500 mg/d *v* gefitinib 250 mg/d or placebo; $P = .0011$ for gefitinib 250 mg/d *v* placebo), defined skin events ($P = .0001$ for gefitinib 500 mg/d *v* gefitinib 250 mg/d; $P < .0001$ for gefitinib 500 mg/d or gefitinib 250 mg/d *v* placebo), and CTC grade 3 and 4 infectious events (predominantly sepsis and febrile neutropenia, rather than any specific or localized infections; $P =$ not significant for gefitinib 500 mg/d *v* gefitinib 250 mg/d; $P = .0099$ for gefitinib 500 mg/d *v* placebo; $P = .022$ for gefitinib 250 mg/d *v* placebo). No adjustments were made to the P values in these analyses to take account of the multiple comparisons.

Posthoc analyses were performed to assess the survival status for patients with specific rash and diarrhea events. The first analysis was performed in a subgroup of patients with any CTC grade event with Coding Symbols for a Thesaurus of Adverse Reaction Terms of acne, rash, or dry skin. The second analysis was performed in a subgroup of patients with CTC grade ≥ 2 events (specifically acne, rash, dry skin, and diarrhea). Neither posthoc analysis showed a difference in overall survival between the three treatment groups.

Only six deaths were considered to be drug-related: three patients in the gefitinib 500 mg/d arm (sudden death, intestinal obstruction, and dehydration plus kidney failure); one in the gefitinib 250 mg/d arm (pulmonary embolus); and two in the placebo arm (sepsis and cerebral vascular accident). The type of adverse events leading to withdrawal were similar in all three treatment groups, the most common being diarrhea. Fewer patients discontinued therapy because of adverse events (any cause) in the ge-

Table 4. Duration of Therapy, Dose Adherence, and Dose-Intensity

	Gefitinib 500 mg/d (n = 342)	Gefitinib 250 mg/d (n = 342)	Placebo (n = 341)
Gefitinib			
Median duration of gefitinib/placebo therapy, days	99	129	138
Dose interruption, %*	55.0	26.3	20.5
Dose reduction, %*	28.9	8.2	3.2
Median dose adherence, %	92.2	98.9	99.5
Chemotherapy			
Median no. of chemotherapy cycles	5	5	6
Paclitaxel median dose-intensity, %	95.3	96.0	96.1
Carboplatin median dose-intensity, %	85.8	87.4	88.5

NOTE. Data are for population assessable for safety.
*Percentage of patients with at least one dose interruption or reduction.

Table 5. Skin Reactions by Grade

	% of Patients		
	Gefitinib 500 mg/d (n = 342)	Gefitinib 250 mg/d (n = 342)	Placebo (n = 341)
Rash			
None	26.0	40.0	55.1
Grade 1	32.2	40.4	32.0
Grade 2	29.8	15.8	11.4
Grade 3	11.1	3.8	1.5
Grade 4	0.9	0	0
Acne			
None	73.1	79.0	90.6
Grade 1	10.5	14.0	7.3
Grade 2	11.4	6.1	2.1
Grade 3	4.4	0.9	0
Grade 4	0.6	0	0
Rash or acne			
None	20.8	33.6	51.9
Grade 1	33.0	42.1	33.7
Grade 2	31.6	19.6	12.9
Grade 3	13.7	4.7	1.5
Grade 4	0.9	0	0

fitinib 250 mg/d and placebo groups (10.5% and 7.9%, respectively) than in the gefitinib 500 mg/d group (22.5%).

DISCUSSION

This large, randomized, placebo-controlled trial examined the efficacy and safety of gefitinib in combination with paclitaxel and carboplatin for the front-line therapy of advanced NSCLC. The data from 1,037 patients demonstrate that combination of conventional chemotherapy with gefitinib did not improve patient survival, disease-free survival, or response rate compared with chemotherapy given alone. Results with gefitinib 250 mg/d were similar to those in the placebo arm, whereas gefitinib 500 mg/d tended toward a worse outcome, although it was not statistically different from placebo. Median survival was 8.7, 9.8, and 9.9 months in the gefitinib 500 mg/d, gefitinib 250 mg/d, and placebo arms, respectively. These results are disappointing and surprising in view of recent results obtained with the phase II studies of single-agent gefitinib in recurrent NSCLC (IDEAL 1 and 2). Tumor response rates of 11.8% to 18.4% and a clinically meaningful symptom improvement of approximately 40% were reported [9,11]. However, in contrast to the current study in chemotherapy-naive patients, the phase II studies recruited patients with recurrent or refractory disease after prior chemotherapy regimens that included platinum. It has yet to be determined whether this difference in patient population alone influenced the lack of additional response seen in our study. It could be speculated that recurrent NSCLC uses EGFR ligands as potential survival factors after platinum-based chemotherapy, as it has been reported that EGF stimulates production of the survival factor vascular endothelial growth factor [21,22]. Recent results show that two phase III trials of first-line erlotinib in combination with standard chemotherapy in patients with metastatic NSCLC did not meet their primary end point of improving overall survival.

Table 6. Pulmonary Adverse Events

	Gefitinib 500 mg/d (n = 342)	Gefitinib 250 mg/d (n = 342)	Placebo (n = 341)
Dyspnea, %	34.2	36.5	32.6
Cough, %	26.6	27.8	24.3
Pneumonia, %	8.5	8.2	8.5
ILD event, n	5	7	3

Abbreviation: ILD, interstitial lung disease.

The current results are also surprising given the striking results reported for gefitinib in combination with chemotherapy in animal models [13,14]. Given our findings, the relevance of animal models to human cancers should be carefully examined, as experimental preclinical results frequently do not translate to the clinic. One factor is the lower doses of chemotherapy agents often used in animal models to observe a synergy with biologic therapies. We used the maximum therapeutic dose of carboplatin and paclitaxel in this human trial, which might have negated this effect. Another limitation is related to tumor implantation in the animal models. Rather than orthotopic tumors, most researchers use subcutaneous ectopic tumor implants, which are devoid of interaction with the true microenvironment of lung cells, and this could specifically alter tumor growth in vivo and perhaps the response to these agents [23,24]. Additionally, many of these cells are implanted only a short time before the start of therapy, which is, of course, much different from the human situation. These unrealistic growth patterns may also alter the response to therapy. Interestingly, the subset analysis of adenocarcinoma patients who received $\geq$ 90 days of chemotherapy suggests that patients receiving gefitinib 250 mg/d who completed therapy had some long-term survival benefits, indicating that gefitinib might be effective as a cytostatic agent in humans, maintaining tumor regression after chemotherapy. This may be due to the ability of gefitinib to block EGFR-dependent survival pathways or possibly due to enhancement of apoptosis. However, this was not seen to the same significant extent in INTACT 1 [16]. These analyses were done posthoc and suffer from selection factors. Furthermore, as many analyses were performed for different subgroups, it is possible that observed effects could have appeared by chance alone. Perhaps the best use of gefitinib in vivo will be in sequence with chemotherapy. This hypothesis can be tested in randomized trials, and plans are underway to initiate such trials. Several options exist, in-

Table 7. Common Drug-Related* Adverse Events (% of patients)

	% of Patients					
	Gefitinib 500 mg/d (n = 342)		Gefitinib 250 mg/d (n = 342)		Placebo (n = 341)	
	All	Grade 3 or 4	All	Grade 3 or 4	All	Grade 3 or 4
Diarrhea	69.3	25.4	58.2	9.9	29.3	2.9
Rash	67.3	11.7	54.4	3.2	37.5	1.5
Acne	26.3	5.0	19.9	0.9	7.3	0
Dry skin	25.7	1.5	15.2	0.3	4.4	0
Pruritus	20.5	1.8	15.2	0.6	12.6	0.3
Nausea	18.7	4.1	19.3	1.8	14.7	2.1
Vomiting	12.9	2.9	11.7	2.0	9.4	2.3
Anorexia	11.7	0.6	7.0	0.6	6.2	0.3
Asthenia	11.1	2.3	13.5	0.3	10.3	1.2
Dehydration	9.9	5.0	3.8	1.8	2.9	1.8
Neutropenia	7.0	6.1	7.9	6.7	5.9	5.9
Anemia	6.7	1.2	6.4	0.6	2.6	0.6
Neuropathy	4.1	0.9	5.3	0.3	5.9	0.9
Leukopenia	3.2	2.3	5.3	2.0	3.8	2.1
Conjunctivitis	6.4	0.6	5.3	0	3.2	0
Alopecia	1.5	0	4.7	0	4.7	0
Dyspnea	0.9	0.3	0.9	0.6	1.5	0.3

*Possibly related to gefitinib/placebo.

cluding first-line gefitinib followed by chemotherapy, gefitinib maintenance therapy after response to chemotherapy or radiotherapy, or adjuvant gefitinib after surgery or radiotherapy for early-stage disease.

This trial was the first placebo-controlled study to address the question of gefitinib safety, and it confirms the safety profile from phase I and II monotherapy trials. Diarrhea and skin toxicity were milder and less frequently reported in the 250 mg/d dose group than in the 500 mg/d group. The frequency of other gastrointestinal side effects was relatively low and similar to the placebo arm. With the exception of mild-to-moderate diarrhea and skin-related events, the gefitinib 250 mg/d arm exhibited a safety profile similar to the placebo arm. Recently, ILD has been reported for four of 18 patients treated with gefitinib for NSCLC, two of whom died [25]. The same incidence was not seen in this randomized controlled study, in which the incidence of ILD-type events was similar in all treatment arms. The favorable tolerability of gefitinib is further supported by the high overall dose adherence. In addition, no change of the expected chemotherapy-related toxicity was observed in the gefitinib-treated arms. Other than dose-response effects, no predisposition factors for gefitinib toxicity were identified, and it can be concluded that gefitinib 250 mg/d has an acceptable safety profile when administered alone or in combination with chemotherapy. Similar results were seen in the INTACT 1 study [16].

Another possible explanation for the lack of a survival difference seen in this study is that patients were not selected on entry for sensitivity to the study agent (in large part because a sensitivity assay does not yet exist). High expression of EGFR has been associated with lower relapse-free and overall survival rates in several malignancies in retrospective studies [26]. However, sensitivity to anti-EGFR therapy does not seem to be correlated with expression of this receptor [27], and conflicting results regarding the relationship between receptor expression and the efficacy of gefitinib have been reported [14,28-31]. It is possible that only patients with upregulated signal transduction pathways along the EGFR axis, such as the Akt pathway, might benefit. Patient selection was important in the use of trastuzumab in metastatic breast cancer, where a positive result with chemotherapy was seen in the subgroup of patients who had significant overexpression of the target [32].

At this time there is no standard method to detect EGFR, HER2, and their phosphorylated forms. Evaluation of the biology of NSCLC tumors treated with gefitinib is currently underway to identify the targets and mechanisms of response and resistance to therapy. Results from the 480 samples collected from patients enrolled in this study will be provided in a separate report. Exploratory analysis of tumor biopsies taken from patients in the IDEAL 1 and 2 trials used a reproducible immunohistochemical assay to estimate the correlation of EGFR membrane staining intensity (no, weak, moderate, or strong staining [0, 1+, 2+, 3+, respectively]) with the probability of objective tumor response or symptom improvement, with the null hypothesis that membrane staining intensity is not predictive of clinical outcome [33,34]. The mean proportion of cells staining 2+ or 3+ was 31.3% for patients with response and 37.5%

for those without response. Furthermore, in both IDEAL trials, five (15%) of 34 patients had response with less than 10% detectable staining. The mean percentage with 3+ staining was 32.1% for patients with and 22.8% for patients without symptom improvement. Therefore, the results of this analysis did not reveal a consistent association between EGFR membrane staining and either objective response or symptom improvement.

Although the current INTACT 2 study did not show superior efficacy when gefitinib was added to paclitaxel and carboplatin, the overall safety profile of gefitinib was confirmed. These data contribute to a better understanding of the optimal use of gefitinib as monotherapy in refractory disease and potentially in sequence with chemotherapy for previously untreated patients with NSCLC.

Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant within the last 2 years: Giuseppe Giaccone, AstraZeneca; Roy S. Herbst, AstraZeneca; Christian Manegold, AstraZeneca; Giorgio Scagliotti, AstraZeneca; Joan Schiller, AstraZeneca; Ronald Natale, AstraZeneca; Vincent Miller, AstraZeneca; David H. Johnson, AstraZeneca. Received more than $2,000 per year from a company for either of the last 2 years: Ronald Natale, AstraZeneca; Vincent Miller, AstraZeneca.

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ORIGINAL REPORT

Gefitinib in Combination With Gemcitabine and Cisplatin in Advanced Non–Small-Cell Lung Cancer: A Phase III Trial—INTACT 1

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ABSTRACT

Purpose
The purpose of this study was to determine whether the addition of the epidermal growth factor receptor tyrosine kinase inhibitor gefitinib (Iressa, ZD1839; AstraZeneca, Wilmington, DE) to standard first-line gemcitabine and cisplatin provides clinical benefit over gemcitabine and cisplatin alone in patients with advanced or metastatic non–small-cell lung cancer (NSCLC). Gefitinib has demonstrated encouraging efficacy in advanced NSCLC in phase II trials in pretreated patients, and a phase I trial of gefitinib in combination with gemcitabine and cisplatin showed favorable tolerability.

Patients and Methods
This was a phase III randomized, double-blind, placebo-controlled, multicenter trial in chemotherapy-naive patients with unresectable stage III or IV NSCLC. All patients received up to six cycles of chemotherapy (cisplatin 80 mg/m^2 on day 1 and gemcitabine 1,250 mg/m^2 on days 1 and 8 of the 3-week cycle) plus either gefitinib 500 mg/d, gefitinib 250 mg/d, or placebo. Daily gefitinib or placebo was continued until disease progression. End points included overall survival (primary), time to progression, response rates, and safety evaluation.

Results
A total of 1,093 patients were enrolled. There was no difference in efficacy end points between the treatment groups: for the gefitinib 500 mg/d, gefitinib 250 mg/d, and placebo groups, respectively, median survival times were 9.9, 9.9, and 10.9 months (global ordered log-rank [GOLrank] $P = .4560$), median times to progression were 5.5, 5.8, and 6.0 months (GOLrank; $P = .7633$), and response rates were 49.7%, 50.3%, and 44.8%. No significant unexpected adverse events were seen.

Conclusion
Gefitinib in combination with gemcitabine and cisplatin in chemotherapy-naive patients with advanced NSCLC did not have improved efficacy over gemcitabine and cisplatin alone. The reasons for this remain obscure and require further preclinical testing.

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INTRODUCTION

Platinum-based combination chemotherapy constitutes standard treatment for patients with advanced or metastatic non–small-cell lung cancer (NSCLC) and a good performance status. Chemotherapy has demonstrated modest but significant improvements in survival rates over best supportive care [1]. However, the prognosis for patients receiving platinum-based chemotherapy as first-line treatment for advanced NSCLC remains poor and side effects are considerable [2]; therefore, novel agents are urgently needed for this disease. One of the most widely used platinum-based combinations is gemcitabine and cisplatin. In two phase III studies of chemotherapy-naive patients with advanced NSCLC, the response rates for patients receiving gemcitabine and cisplatin were 30.4% to 40.6%, median times to

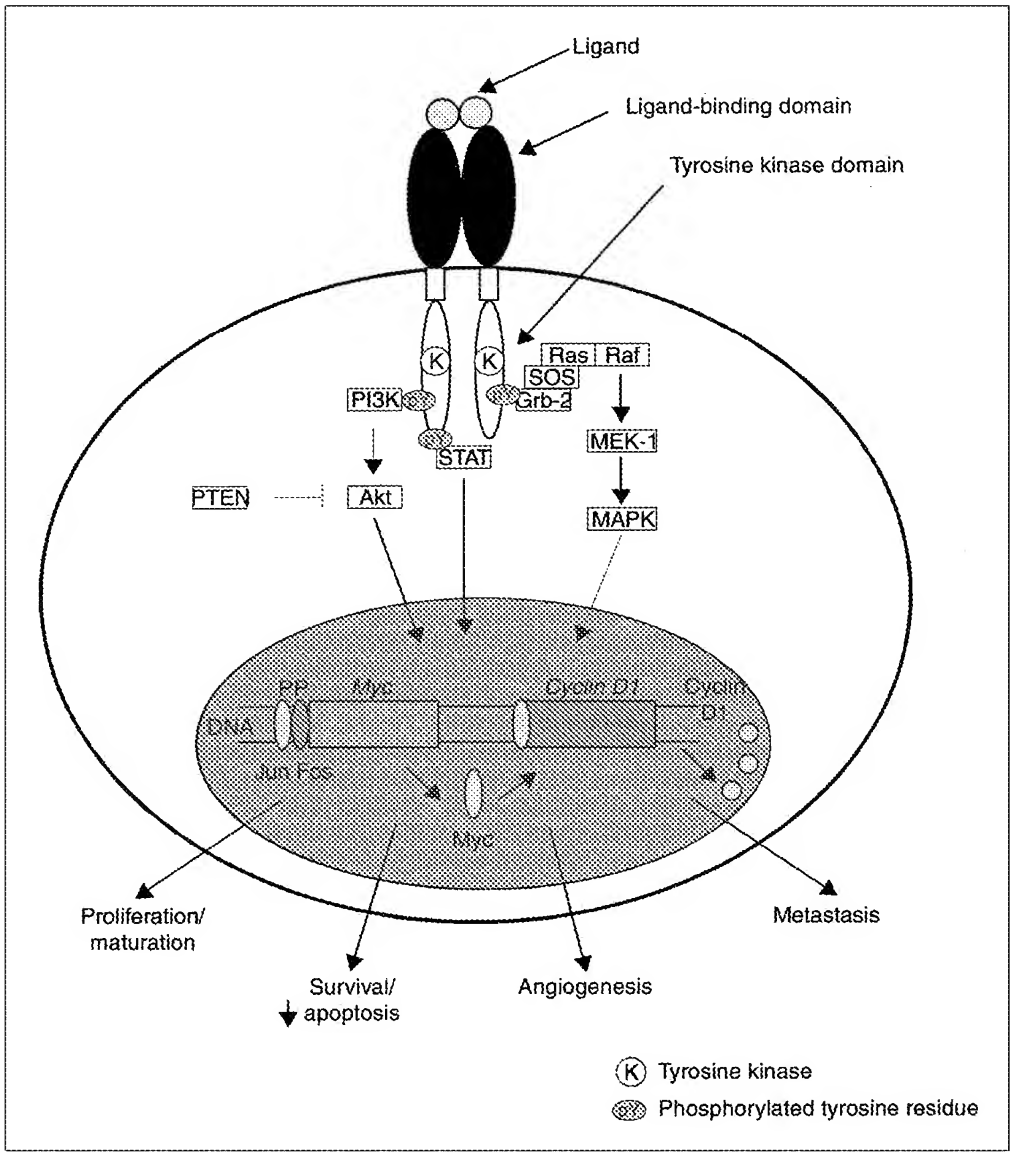

Fig 1. Epidermal growth factor receptor signal transduction. Adapted with permission [5].

progression were 5.6 to 6.9 months, and overall survival times were 8.7 to 9.1 months [3,4].

The epidermal growth factor receptor (EGFR) has been shown to play an important role in the growth and survival of many solid tumors, including NSCLC. Activation of EGFR enhances the processes responsible for tumor growth and progression, including the promotion of proliferation, angiogenesis, and invasion/metastasis and inhibition of apoptosis (Fig 1) [5-7]. Gefitinib (Iressa, ZD1839; AstraZeneca, Wilmington, DE) is an orally active EGFR tyrosine kinase inhibitor (EGFR-TKI) that blocks the signal transduction pathways implicated in the proliferation and survival of cancer cells [7].

Two phase II trials of gefitinib monotherapy in patients with pretreated advanced NSCLC demonstrated encouraging antitumor activity (objective response rates, 11.8% to 18.4%) and symptom relief (symptom improvement rates, 40.3% to 43.1%) and good tolerability [8-11]. This favorable tolerability profile, coupled with its mechanism of action, which is distinct from that of cytotoxic agents, provides a strong rationale for use of gefitinib in combination with standard cytotoxic regimens. This rationale is supported by data from preclinical studies in which gefitinib potentiated the efficacy of various cytotoxic drugs against a range of human solid tumor types, both in vitro and in vivo [12,13]. In particular, synergy was observed when gefitinib and cisplatin were used in combination, whereas no synergy could be demonstrated between gemcitabine and gefitinib [13].

On the basis of phase I trials of gefitinib monotherapy, two doses were identified for further study based on pharmacokinetics and clinical activity. Gefitinib 250 mg/d is higher than the lowest dose at which clinical responses were

seen (150 mg/d), and 500 mg/d is the highest dose level that is well tolerated for a long period by most patients. A feasibility study of daily oral gefitinib (250 and 500 mg/d) in combination with gemcitabine and cisplatin demonstrated a manageable and predictable tolerability profile with no evidence of any clinically significant pharmacokinetic interactions between gefitinib and cisplatin or gemcitabine [14]. Encouraging antitumor activity was seen in a range of solid tumors at both gefitinib doses in this study [14].

Here we present the results from a multinational, randomized, double-blind, placebo-controlled phase III study. The Iressa NSCLC Trial Assessing Combination Treatment (INTACT) 1 investigated the efficacy and safety of gefitinib (250 and 500 mg once daily) versus placebo in combination with cisplatin plus gemcitabine in chemotherapy-naive patients with advanced NSCLC. The primary objective was to assess whether gefitinib increases overall survival relative to placebo in combination with cisplatin and gemcitabine. A second trial of identical design (INTACT 2) has been conducted to investigate gefitinib in combination with paclitaxel plus carboplatin, another commonly used combination in patients with advanced NSCLC [15].

PATIENTS AND METHODS

Patients were randomly assigned to one of three treatment groups in a double-blind manner. All patients received gemcitabine and cisplatin in combination with gefitinib 500 mg/d, gefitinib 250 mg/d, or placebo. Patients were further stratified by dynamic randomization [16] according to weight loss in previous 6 months ($\leq$ 5% *v* > 5%), disease stage (III *v* IV), performance status (0 to 1 *v* 2), and measurable disease (yes *v* no).

Treatment

Gefitinib or placebo was administered orally, once daily. Chemotherapy was administered in 3-week cycles for a total of six cycles: intravenous gemcitabine 1,250 mg/m^2 for 30 minutes on days 1 and 8; intravenous cisplatin 80 mg/m^2 after gemcitabine administration on day 1 only. Subsequently, patients continued on gefitinib or placebo until disease progression. One gefitinib/placebo dose reduction (500 to 250 mg/d or 250 to 100 mg/d) was allowed per patient. In the event of grade 3 or 4 adverse events not thought to be due to disease progression or gemcitabine and cisplatin, gefitinib administration could be interrupted for a maximum of 14 days.

Eligibility Criteria

The inclusion criteria included histologically/cytologically confirmed NSCLC, locally advanced stage III disease not curable with surgery or radiotherapy or stage IV disease, aged $\geq$ 18 years, and WHO performance status of 0 to 2. Patients were not eligible for this trial if they had previously received chemotherapy (prior surgery or localized radiation were allowed); were hypersensitive to mannitol, corticosteroids, H_2-antagonists, antihistamines or agents formulated with polyoxyethylated castor oil; had received radiotherapy within the last 2 weeks; had unresolved toxicity from previous radiation therapy or incomplete healing from previous surgery; had preexisting motor or sensory neurotoxicity (National Cancer Institute Common Toxicity Criteria $\geq$ grade 2); showed evidence of severe or uncontrolled systemic disease; had recent conditions requiring medication or uncontrolled significant active infections; had an absolute neutrophil count less than 2,000/mm^3, WBCs less than 4,000/mm^3, or platelets less than 100,000/mm^3; had serum bilirubin greater than 1.25 times the upper limit of reference range (ULRR), ALT or AST greater than 2.5 times ULRR (five times ULRR in the presence of liver metastases), serum creatinine greater than 1.5 times ULRR, or creatinine clearance less than 60 mL/min; were pregnant or breast-feeding; had other coexisting malignancies or malignancies diagnosed within the last 5 years with the exception of basal-cell carcinoma or cervical cancer in situ; or had mixed NSCLC plus small-cell lung cancer. Patients with stable brain metastasis or spinal-cord compression were eligible. All patients signed a written informed consent form, and trial approval was obtained from the ethics committee at each trial center. The study followed the Declaration of Helsinki [17] and good clinical practice guidelines.

Assessments

Overall survival and time to progression were assessed from the date of randomization to the date of patient death and the date of objective disease progression (death was considered a progression event in those patients who died before disease progression), respectively. Patients without documented death or objective progression at the time of the final analysis were censored at the date they were last known to be alive or of their last objective tumor assessment, respectively. Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors [18]. During the trial and for 30 days after the last dose of gefitinib or placebo, patients were monitored for adverse events, which were graded according to the National Cancer Institute Common Toxicity Criteria. Hematology and biochemistry assessments were performed $\leq$ 7 days before the date of randomization and at each clinic visit.

Statistical Analysis

An Independent Data Monitoring Committee provided ongoing guidance and recommendations for patient management, based on review of the formal interim efficacy analysis, and also reviewed safety data on an ad-hoc basis, as determined by a steering committee. The role of the committee was to provide executive oversight and supervision for the conduct of the trial, through review of trial enrollment, protocol and clinical conduct, and blinded safety data.

Gefitinib was compared with placebo on an intent-to-treat basis with respect to overall survival. The study was designed to have 90% power for a two-sided overall significance level test of the hypothesis that gefitinib increases survival relative to placebo given a hazard ratio of 1.33. Assuming a 1-year survival rate of 30% in the placebo arm, this hazard ratio equates to an increase in median survival of 2.3 months for both gefitinib arms. The final analysis of overall survival was planned to include 750 events. On the basis of the study design assumptions, 1,029 patients were required.

An adaptive survival analysis procedure was used at the final analysis that tested either for a positive or negative gefitinib dose-response relationship based on prospective criteria applied to the observed data. A survival trend test (global ordered log-rank test [GOLrank]) was to be used for a positive dose-response relationship, whereas pairwise log-rank tests would be used for a mixed dose-response relationship [19]. To preserve an overall two-sided 5% significance level, and to account for the use of a GOLrank test

at an interim analysis, simulations with the adaptive procedure were used to calculate a nominal significance level of 4.4% for the final analysis. According to prospective criteria for the adaptive procedure, the final analysis used a GOLrank test to compare survival between the treatment arms.

A posthoc multivariate analysis with eight prespecified prognostic factors at trial entry (disease stage III *v* IV; performance status 0 or 1 *v* 2; weight loss in prior 6 months $\leq$ 5% *v* > 5%; sex; histology; presence or absence of metastases to bone, liver, or brain) was performed to assess which variables predicted improved survival.

In a posthoc subgroup analysis, stratification and prognostic factors (disease stage III *v* IV; performance status 0 or 1 *v* 2; weight loss in prior 6 months $\leq$ 5% *v* > 5%; presence or absence of metastases to bone, liver, or brain) and subgroups of sex and histology were examined in a univariate model. An unadjusted Cox proportional hazard test was applied to the overall survival data for each subgroup to estimate the hazard ratio and 95% CI for the treatment comparisons of gefitinib 250 or 500 mg/d versus placebo.

RESULTS

Patients

In total, 1,093 patients were enrolled from 155 centers between May 2000 and March 2001. Most patients were enrolled by European trial centers (n = 816; 74.7%), but patients were also enrolled in North America (n = 139; 12.7%), Asia (n = 58; 5.3%), South America (n = 45; 4.1%), and South Africa (n = 17; 1.6%). Almost three quarters of the patients were men and the median age was approximately 60 years. Overall, 998 (90.4%) of the patients were white. Most patients had stage IV disease (n = 757; 69.2%) or IIIB with malignant pleural effusion (n = 239; 21.9%). Most patients (n = 984; 90.0%) had a performance status of 0 or 1. The most common histology types were adenocarcinoma and squamous-cell carcinoma, seen in 504 (46.1%) and 328 patients (30.0%), respectively. The three treatment arms were well balanced (Table 1). The median follow-up duration was 15.9 months.

Table 1. Patient Demographics

	Gefitinib 500 mg/d (n = 365)	Gefitinib 250 mg/d (n = 365)	Placebo (n = 363)
Sex, %			
Female	27.9	23.3	27.8
Male	72.1	76.7	72.2
Age, years			
Median	61	59	61
Range	31-85	34-83	33-81
Disease stage, %*			
IIIa	3.0	1.6	1.9
IIIb	29.9	25.8	28.4
Without pleural effusion	5.5	6.3	6.6
With pleural effusion	24.4	19.5	21.8
IV	66.8	72.3	68.6
WHO performance status, %*			
0	32.1	34.0	33.9
1	58.1	56.4	55.6
2	9.6	9.6	9.6
Weight loss in previous 6 months, %*			
$\leq$ 5%	62.7	64.1	63.9
> 5%	37.0	35.6	35.0
Disease measurability, %*			
Measurable	94.8	94.8	93.4
Nonmeasurable	4.9	4.9	5.8
Histology, %*			
Squamous	28.8	32.1	29.2
Adenocarcinoma	43.3	48.5	46.6
Squamous and adenocarcinoma	2.7	1.4	1.4
Bronchoalveolar	1.1	0.8	0.3
Undifferentiated	11.5	9.3	11.8
Large cell	11.5	7.7	8.8
Race, %			
White	91.0	90.4	89.8
Black	0.8	1.4	1.4
Asian	1.9	1.6	0.8
Hispanic	1.4	2.5	2.2
Oriental	4.9	3.6	5.8
Other	0.0	0.5	0.0
Metastatic disease, %†			
Lung, other	54.9	53.4	51.0
Bone	30.3	34.8	37.8
Liver	21.7	22.3	20.5
Adrenal tissue	21.3	22.7	19.7
Lymph nodes	10.2	10.2	14.1
Skin or soft tissue	5.7	5.3	7.2
Brain	5.3	4.5	2.8
Other	7.8	4.9	4.8

*Information was not available for all patients.
†Stage IV patients only.

Efficacy

At each interim analysis, the Independent Data Monitoring Committee recommended that the trial continue. At the time of this analysis, 732 and 628 events were observed for survival and time to progression, respectively, with a minimum follow-up of 12 months for overall survival and 6 months for all other end points. There was no statistically significant difference in overall survival between each of the gefitinib arms and the placebo arm. The median survival times were 9.9 months for each of the gefitinib groups, and 10.9 months for the placebo group (GOLrank P = .4560; Fig 2). One-year survival rates were 43% and 41% for the 500 mg/d and 250 mg/d gefitinib groups, respectively, and 44% for the placebo group. Similarly, median time to progression was 5.5 and 5.8 months for the 500 mg/d and 250 mg/d gefitinib groups, respectively, and 6.0 months in the placebo group, with no statistically significant difference between treatment arms (GOLrank P = .7633; Fig 3). In the posthoc multivariate analysis, a performance status of 2, weight loss, and bone and liver metastases were significant (P < .05) predictors of worse survival outcome. In the posthoc univariate analysis examining known NSCLC prognostic factors and subgroups of sex, time on chemotherapy, and histology, no survival differences were seen

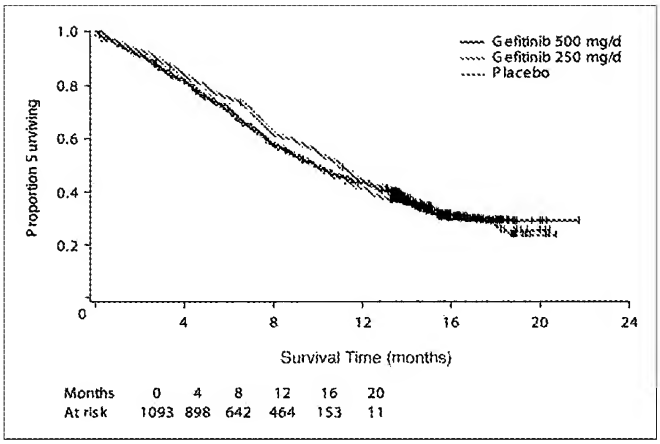

Fig 2. Kaplan-Meier estimates of overall survival in each treatment group. (global ordered log-rank $P = .4560$).

between treatments for any subgroups of patients [20]. Objective tumor response rates were 50.3% and 51.2% for the 500 mg/d and 250 mg/d gefitinib groups, respectively, and 47.2% in the placebo group (P = not significant). Very few complete responses were seen (Table 2).

Duration of Therapy, Dose Intensity, and Dose Adherence

The dose-intensity of both gemcitabine and cisplatin was similar in all three treatment groups (Table 3), demonstrating that chemotherapy dose intensity was not compromised by the addition of gefitinib. There was a high overall adherence to gefitinib; however, most gefitinib dose interruptions and reductions were seen in the gefitinib 500 mg/d arm (the number was similar in the gefitinib 250 mg/d and placebo arms) [Table 3]. Patients receiving gefitinib 250 mg/d or placebo had a longer therapy duration than those receiving gefitinib 500 mg/d.

Safety and Tolerability

Most adverse events occurred during the combination phase of the trial and many were consistent with the known

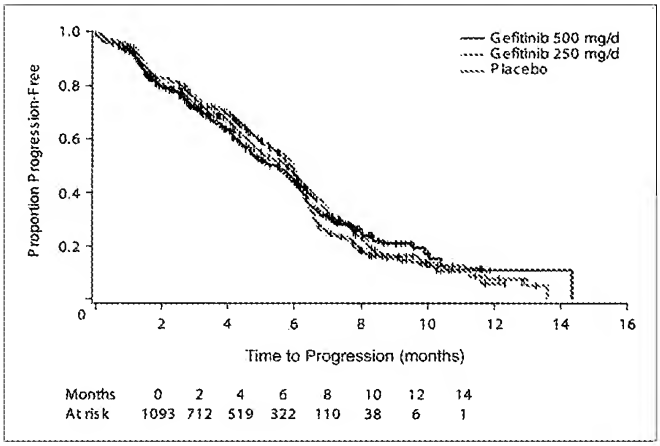

Fig 3. Kaplan-Meier estimates of time to progression in each treatment group. (global ordered log-rank $P = .7633$).

Table 2. Objective Tumor Responses in Each Treatment Group (population assessable for tumor response)

	Objective Tumor Response (%)		
	Gefitinib 500 mg/d (n = 330)	Gefitinib 250 mg/d (n = 336)	Placebo (n = 324)
Complete response	2.1	3.3	0.9
Partial response	48.2	47.9	46.3
Response rate (complete plus partial response)	50.3	51.2	47.2

toxicities of the chemotherapy agents. Overall, the safety data from the monotherapy period of the trial support the gefitinib safety profile previously established in phase I and II trials. The most commonly occurring adverse events were gastrointestinal, skin-related, or hematologic in nature. Statistical analysis of prespecified adverse events during the chemotherapy phase revealed no difference between treatment arms except for diarrhea and skin events (diarrhea $P < .0001$ for 500 mg/d v 250 mg/d or placebo; $P = .0924$ for 250 mg/d v placebo; defined skin events $P < .0001$ for all comparisons [no adjustments were made to the P values to take account of the multiple comparisons]), which are known to be associated with gefitinib treatment. A clear dose-response relationship was observed for these events. Interstitial lung disease (ILD)–type events were experienced by three, one, and three patients in the gefitinib 500 mg/d, gefitinib 250 mg/d, and placebo arms, respectively, giving an overall incidence of less than 1%. The incidence of ILD-type events and other respiratory events that were possibly indicative of ILD is summarized in Table 4. No difference in reports of symptoms possibly related to, or indicative of, ILD (eg, dyspnea, increased cough, pneumonia) was seen between the groups.

The most frequently occurring adverse events considered by the investigators to be related to gefitinib/placebo treatment were rash, diarrhea, and acne, which were generally mild (grade 1 or 2; Table 5). No significant additive toxicity was evident in this placebo-controlled setting. Deaths and withdrawals owing to gefitinib/placebo-related toxicity were low and balanced between the three treatment arms. The proportion of patients withdrawn from treatment because of adverse events of any cause was higher (23.0%) for patients in the 500 mg/d group, compared with 14.5% and 11.3% for 250 mg/d and placebo groups, respectively. The types of events leading to withdrawal were similar across the three groups: diarrhea, nausea, vomiting, and acne-like rash.

DISCUSSION

In this study, gefitinib showed no survival benefit over placebo when combined with gemcitabine and cisplatin in a large population of chemotherapy-naive patients with advanced NSCLC. Furthermore, gefitinib did not improve

Table 3. Duration of Therapy, Dose Adherence, and Dose Intensity (population assessable for safety)

	Gefitinib 500 mg/d (n = 358)	Gefitinib 250 mg/d (n = 362)	Placebo (n = 355)
Gefitinib			
Median duration of gefitinib/placebo therapy, days	97	150	159
Dose interruption, %*	45.8	26.8	17.2
Dose reduction, %*	23.2	6.4	2.8
Median dose adherence, %	91.8	97.7	99.5
Chemotherapy			
Median No. of chemotherapy cycles	4	6	6
Gemcitabine median dose-intensity, %	84.2	84.6	85.9
Cisplatin median dose-intensity, %	92.0	91.9	92.4

*Percentage of patients with at least one dose interruption or reduction.

time to progression or objective tumor response over chemotherapy alone. Similar results were seen in the twin study INTACT 2, in which gefitinib was evaluated in combination with paclitaxel and carboplatin [15]. These results are disappointing and surprising because of the significant antitumor activity of gefitinib when given alone to pretreated patients with advanced NSCLC [9,11] and because additive or synergistic activities of gefitinib and several chemotherapeutic drugs have been seen in preclinical models [12]. However, it should be noted that phase II data were not available when these studies were initiated.

The results of two similar trials investigating the use of another EGFR-TKI, erlotinib, in combination with gemcitabine and cisplatin or paclitaxel and carboplatin, have recently been reported. As in our study, the addition of an EGFR-TKI to first-line chemotherapy in patients with advanced NSCLC did not result in any improvement in overall survival over chemotherapy alone.

No significant adverse events were seen that were not predictable from the safety profiles of gefitinib monotherapy and gemcitabine and cisplatin. Furthermore, the safety profile was similar for all treatment arms, with the exception of dose-related additive diarrhea and skin toxicity. As in the phase II gefitinib monotherapy trials, more dose interruptions and reductions of gefitinib were seen in the 500 mg/d arm. Furthermore, although the chemotherapy dose-intensity was similar across the treatment arms, patients on the 500 mg/d arm received a lower median number of chemotherapy cycles. This may have been due to a higher degree of antagonism occurring in this arm, leading to earlier disease progression. These results confirm, in a placebo-controlled setting, that gefitinib has a favorable safety profile and that 250 mg/d is better tolerated than 500 mg/d. Recently published data suggest that gefitinib might be associated with interstitial pneumonia [21]; however, in our study, the overall incidence of ILD was less than 1%, and no imbalance was identified across the three treatment arms in terms of pneumonitis/ILD-type events. One patient receiving gefitinib 250 mg/d and three patients each in the gefitinib 500 mg/d and placebo groups were reported to have experienced an ILD-type event. Furthermore, there was no difference between arms in reports of symptoms possibly related to, or indicative of, ILD, such as dyspnea, cough, or pneumonia. Interestingly, the frequency of ILD-type events in patients receiving gefitinib seems to be higher in Japanese patients (1.9%) than in the rest of the world (0.34%; data on file, AstraZeneca, Wilmington, DE). As yet, the reason for this is unknown, although it may be related to population or environmental differences, or differences in clinical practice.

Table 4. Pulmonary Adverse Events (population assessable for safety)

	Gefitinib 500 mg/d (n = 358)	Gefitinib 250 mg/d (n = 362)	Placebo (n = 355)
Dyspnea, %	17.9	17.7	23.1
Cough, %	15.4	17.7	18.3
Pneumonia, %	3.9	5.5	4.8
ILD event, n	3	1	3

Abbreviation: ILD, interstitial lung disease.

The reasons for the disappointing efficacy results are still unclear. It is possible that each of the agents is working against a susceptible subpopulation of tumor cells so that the effect is redundant rather than additive, or that one agent results in the loss of an intermediary molecule that is essential to the function of the other agent, resulting in an antagonistic effect.

Patients included in this study and all other studies with gefitinib were not selected on the basis of presence of the target EGFR. Samples from approximately one third of the patients accrued in the study are being immunohistochemically assessed for expression of the receptor. Of course it is conceivable that if only a small number of patients are sensitive to gefitinib, the diluting effect of the lack of selection might make it impossible to discern small differences. A sharper definition of such susceptible subgroups of patients will certainly help in further develop-

Table 5. Commonly Occurring Gefitinib/Placebo-Related Adverse Events (population assessable for safety)

	Adverse Event (%)					
	Gefitinib 500 mg/d (n = 358)		Gefitinib 250 mg/d (n = 362)		Placebo (n = 355)	
	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4
Rash	56.7	12.6	44.5	3.6	21.4	1.1
Diarrhea	50.8	12.0	28.7	3.6	15.5	2.3
Acne	28.2	5.9	18.2	1.4	5.1	0.3
Nausea	19.0	4.5	17.1	2.5	17.5	2.0
Vomiting	17.0	4.7	13.8	2.8	12.4	2.3
Pruritus	12.6	2.0	7.5	0	7.0	0
Asthenia	10.9	2.2	9.7	1.9	10.1	0.8
Dry skin	9.5	0	7.2	0	3.1	0
Anorexia	7.0	1.7	5.2	0.6	4.8	0.3
Thrombocytopenia	7.0	4.2	7.7	5.8	7.9	5.6
Anemia	5.0	2.5	3.9	1.9	6.2	1.7
Neutropenia	5.0	5.0	5.0	5.8	7.0	4.8
Leukopenia	3.9	2.0	2.0	3.3	4.5	2.5
Conjunctivitis	5.3	0.3	0.3	2.5	2.8	0

ment of this type of agent, for which the expression of the target is unlikely to accurately predict the activity of the therapy. In fact, the level of expression of EGFR was not predictive of the sensitivity to gefitinib in a number of in vitro systems [22], and immunohistochemical analysis of samples from the two phase II trials of gefitinib monotherapy in patients with pretreated advanced NSCLC did not provide any evidence of a correlation between EGFR expression levels and either response or symptom improvement. Indeed, substantial numbers of EGFR-negative patients benefited from gefitinib, whereas some patients with intense EGFR staining did not show any response [23].

It seems that inhibition of EGFR autophosphorylation rather than expression of the receptor might impact on the activity of this agent. Furthermore, the assessment of pathways downstream from the activation cascade of EGFR (PI3K/Akt and Ras/Erk) might give more insight into the possibility of inactivating the receptor cascade.

Because no additive effect was observed by administering gefitinib continuously in combination with chemotherapy, possible alternatives could be the administration of gefitinib in the interval between chemotherapy cycles or as maintenance treatment after chemotherapy. This could also potentially prevent the problem of drug interference or antagonism.

In conclusion, INTACT 1 did not show superior efficacy of gefitinib added to gemcitabine and cisplatin in patients with advanced NSCLC. Previous studies have shown that gefitinib is an active agent for a number of patients with advanced NSCLC, so further work is needed to identify subsets of patients who may benefit more from this therapy. Additional preclinical studies may shed light on the lack of additive or synergistic activity in unselected human tumors.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant within the last 2 years: Giuseppe Giaccone, AstraZeneca; Roy S. Herbst, AstraZeneca; Christian Manegold, AstraZeneca; Giorgio Scagliotti, AstraZeneca; Joan Schiller, AstraZeneca; Ronald Natale, AstraZeneca; Vincent Miller, AstraZeneca; Ulrich Gatzemeier, AstraZeneca; David H. Johnson, AstraZeneca. Received more than $2,000 per year from a company for either of the last 2 years: Ronald Natale, AstraZeneca; Vincent Miller, AstraZeneca.

Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

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ORIGINAL REPORT

Phase III Study of Erlotinib in Combination With Cisplatin and Gemcitabine in Advanced Non–Small-Cell Lung Cancer: The Tarceva Lung Cancer Investigation Trial

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ABSTRACT

Purpose
Erlotinib is a potent inhibitor of the epidermal growth factor receptor tyrosine kinase, with single-agent antitumor activity. Preclinically, erlotinib enhanced the cytotoxicity of chemotherapy. This phase III, randomized, double-blind, placebo-controlled, multicenter trial evaluated the efficacy and safety of erlotinib in combination with cisplatin and gemcitabine as first-line treatment for advanced non–small-cell lung cancer (NSCLC).

Patients and Methods
Patients received erlotinib (150 mg/d) or placebo, combined with up to six 21-day cycles of chemotherapy (gemcitabine 1,250 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1). The primary end point was overall survival (OS). Secondary end points included time to disease progression (TTP), response rate (RR), duration of response, and quality of life (QoL).

Results
A total of 1,172 patients were enrolled. Baseline demographic and disease characteristics were well balanced. There were no differences in OS (hazard ratio, 1.06; median, 43 *v* 44.1 weeks for erlotinib and placebo groups, respectively), TTP, RR, or QoL between treatment arms. In a small group of patients who had never smoked, OS and progression-free survival were increased in the erlotinib group; no other subgroups were found more likely to benefit. Erlotinib with chemotherapy was generally well tolerated; incidence of adverse events was similar between arms, except for an increase in rash and diarrhea with erlotinib (generally mild).

Conclusion
Erlotinib with concurrent cisplatin and gemcitabine showed no survival benefit compared with chemotherapy alone in patients with chemotherapy-naïve advanced NSCLC.

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INTRODUCTION

Lung cancer is a major cause of morbidity and mortality,[1-4] and the majority of new cases are advanced non–small-cell lung cancer (NSCLC).[5] The standard first-line treatment for advanced NSCLC is a platinum-based two-drug combination regimen.[6] However, no doublet regimen has proved superior,[7-10] and survival outcomes are poor (median survival, 8 to 10 months; 1-year survival rate 35% to 40%).[11] Thus, new, well-tolerated treatments that can improve overall survival (OS) in NSCLC are urgently needed.

The epidermal growth factor receptor (EGFR) has a pivotal role in tumorigenesis,[12-14] with many human cancers overexpressing EGFR,[15-17] including up to 80% of NSCLCs. Overexpression of EGFR is associated with advanced disease and poor survival.[18,19] Erlotinib (Tarceva; F. Hoffmann-La Roche, Basel, Switzerland) is a highly potent, orally active EGFR tyrosine-kinase inhibitor (TKI) that has shown significant antitumor activity in preclinical studies.[20-23] Evidence of antitumor activity with single-agent erlotinib came from phase I/II studies in previously treated patients. In one phase II trial in NSCLC, median OS was 8.4 months and 1-year survival was 40%.[27] Erlotinib was generally well tolerated at 150 mg/d (the maximum tolerated dose).[24-28] In a large phase III trial in previously treated patients with advanced NSCLC, erlotinib significantly prolonged survival versus placebo (6.7 *v* 4.7 months; hazard ratio [HR], 0.70; $P < .001$), delayed disease progression, and delayed worsening of disease-related symptoms.[29,30]

This is the only placebo-controlled trial to have shown prolonged survival with an EGFR inhibitor in advanced NSCLC.

Cisplatin plus gemcitabine is widely used for first-line treatment of advanced NSCLC. In A549 human NSCLC xenografts, erlotinib showed additive effects with gemcitabine, and synergism with cisplatin.[31] Although no phase I/II trials had evaluated the triplet regimen, it was postulated that adding erlotinib could lead to improved efficacy, without significant additional toxicity. The toxicity profile of cisplatin plus gemcitabine (involving neutropenia, thrombocytopenia, nausea, and vomiting[32,33]) is distinct from that of erlotinib. Here we report the results of a phase III, randomized, placebo-controlled trial (Tarceva Lung Cancer Investigation [TALENT]) of cisplatin and gemcitabine with or without erlotinib in patients with previously untreated advanced NSCLC.

PATIENTS AND METHODS

Eligibility Criteria

Entry criteria included histologically documented, unresectable, locally advanced, recurrent or metastatic (stage IIIb/IV) NSCLC; age ≥ 18 years; Eastern Cooperative Oncology Group performance status 0 or 1; and adequate hematologic, renal, and hepatic function. Exclusion criteria included prior chemotherapy/systemic antitumor therapy or exposure to human epidermal growth receptor–directed agents; unstable systemic disease; other malignancies within 5 years; and any significant ophthalmologic abnormalities.

The study was conducted at 164 centers in 27 countries in Europe, Canada, South America, and Australasia. All patients provided written informed consent. Approval was obtained from each center's independent ethics committee. The study conformed to the principles of the Declaration of Helsinki[34] and Good Clinical Practice guidelines.[35]

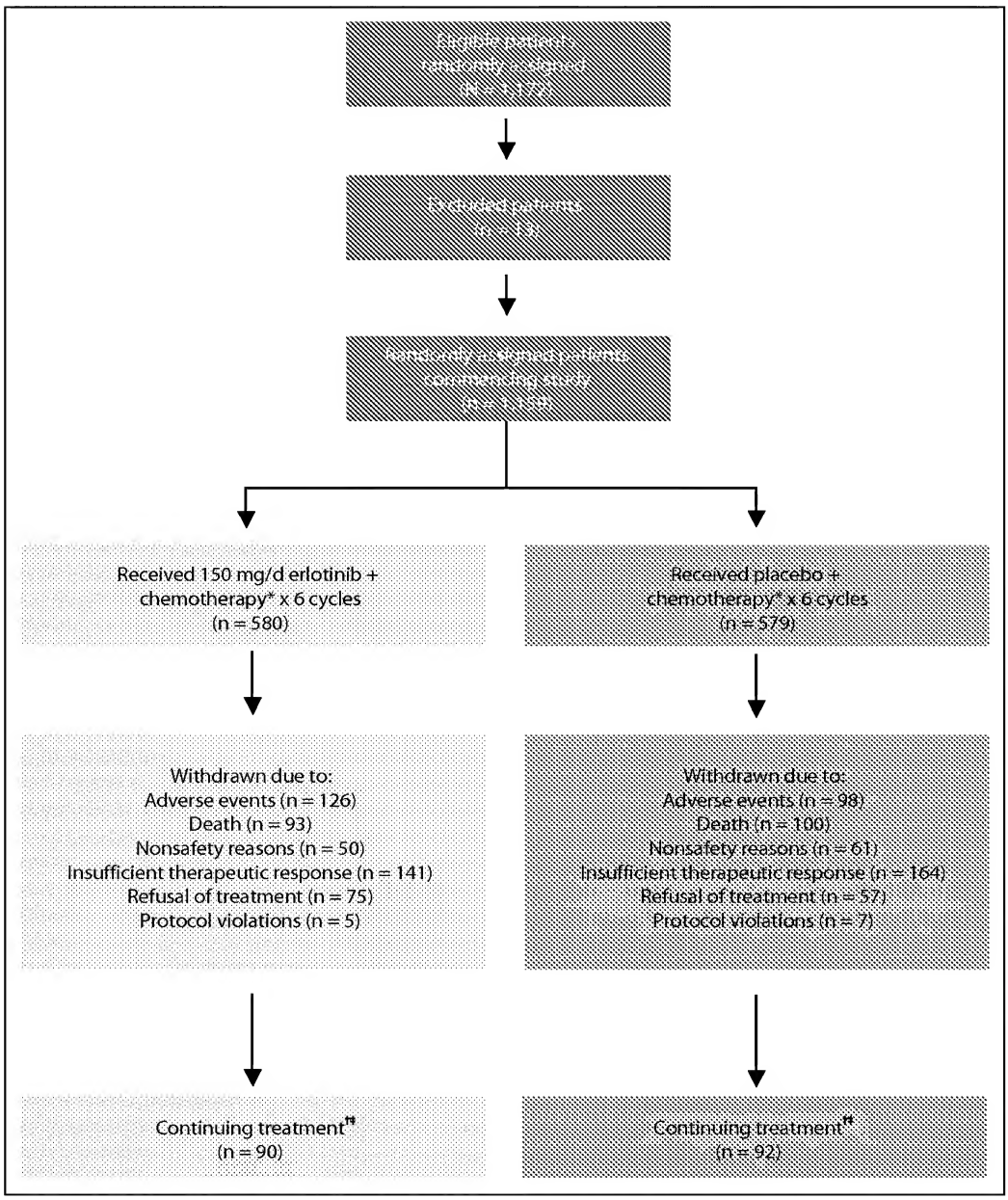

Fig 1. Tarceva Lung Cancer Investigation (TALENT) study schema and patient disposition. *Patients were scheduled to receive gemcitabine 1,250 mg/m^2 on days 1 and 8 on a 3-week cycle and cisplatin 80 mg/m^2 on day 1 every 3 weeks. A maximum of six cycles of chemotherapy, in the absence of disease progression, were planned. †For disease progression, patients could continue receiving either study drug (erlotinib or placebo) in combination with second-line chemotherapy or chemotherapy alone. ‡Treatment continued to data cutoff point on June 30, 2003.

Table 1. Baseline Patient and Disease Characteristics

Parameter	Placebo (n = 579)* No. of Patients	Placebo (n = 579)* %	Erlotinib (n = 580)* No. of Patients	Erlotinib (n = 580)* %
Sex*				
Female	142	25	125	22
Male	437	75	455	78
Age, years*				
Mean	59.1		60.0	
SD	10.01		9.27	
Median	60.0		61.0	
Range	28-84		26-82	
Race/ethnicity*				
White	533	92	531	92
Black	—		3	< 1
Asian	22	4	20	3
Other	24	4	26	4
Baseline ECOG performance status*				
0	176	30	156	27
1	400	69	423	73
2	1	< 1	1	< 1
Cancer stage†				
II	—		1	< 1
IIIB (total)	192	33	207	35
With malignant pleural or pericardial effusion	57	10	52	9
Unresectable	135	23	155	26
IV	393	67	378	65
Not assessed	1	< 1	1	< 1
Tumor type†				
Measurable	536	91	533	91
Nonmeasurable	50	9	53	9
Histology†				
Adenocarcinoma	221	38	224	38
Large cell carcinoma	52	9	58	10
Squamous cell carcinoma	243	41	239	41
Other	70	12	65	11

Abbreviations: SD, standard deviation; ECOG, Eastern Cooperative Oncology Group.
*Patients treated with at least one dose of study drug.
†Randomly assigned patients; n = 586 patients per treatment arm.

Trial Design

In an initial 50-patient safety cohort (to determine the safe dose of erlotinib), patients were randomly assigned to oral erlotinib 100 mg/d or placebo for 7 days before chemotherapy was added. Dose escalation of erlotinib to 150 mg/d started on day 15 of the first cycle, if the initial dose was tolerated. This phase of the trial also involved intense and rapid safety reporting (real-time safety monitoring). When two chemotherapy cycles were complete, safety data were reviewed by an independent Data and Safety Monitoring Board, to assess whether 150 mg/d erlotinib was sufficiently well tolerated for use in the main study.

Patients then received erlotinib 150 mg/d or placebo, in combination with a maximum total of six 21-day cycles of chemotherapy, in the absence of disease progression (Fig 1). Initially, all patients received gemcitabine 1,250 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1 of each cycle. Patients continued to receive erlotinib or placebo until unacceptable toxicity or death. On disease progression, patients could continue with study treatment (erlotinib or placebo), with or without second-line therapy or, alternatively, receive second-line therapy alone.

Assessments

The primary end point was OS (time from random assignment to death, irrespective of cause). Secondary end points included time to disease progression (TTP; time from random assignment to disease progression or death, whichever was first); response rate (RR; according to Response Evaluation Criteria in Solid Tumors)[36]; duration of response; quality of life (QoL); EGFR expression; pharmacokinetic (PK) parameters; and safety.

QoL was evaluated by the time to symptomatic progression (the time from random assignment to the first QoL assessment when symptomatic progression was identified). Symptomatic progression was defined as a worsening from baseline in the average symptom burden index by 25% on the Lung Cancer Symptom Scale.

Where possible, tumor EGFR expression was assessed at baseline by immunohistochemistry (EGFR pharmDx; DakoCytomation, Carpinteria, CA). Samples were scored for membrane staining (0, 1+, 2+, 3+) according to the highest intensity seen in at least 10% of the cells.

PK analysis of erlotinib, gemcitabine, and cisplatin was performed in the initial 50-patient safety cohort (study-intensive PK) and in the main phase of the trial (study-population PK). Study-intensive PK samples were collected predosing and at intervals for 24 hours postdose on days −1, 1, and 7 of cycle 1 for the analysis of erlotinib and its active metabolite, OSI-420. Gemcitabine and cisplatin were analyzed in blood samples collected pre- and postinfusion on day 1 of cycle 1. Study-population PK samples for erlotinib evaluation were taken predose from at least 400 patients on day 1 of cycles 1 to 4.

The first 400 patients randomly assigned in the main phase of the trial underwent intense safety evaluation, with monitoring of adverse events (AEs), laboratory data, population PKs, and PK samples for premature discontinuations, medical resource use, and ophthalmologic examinations. For the remaining patients, safety was monitored using National Cancer Institute Common Toxicity Criteria.

Statistical Analysis

The primary end point was analyzed using a two-sided log-rank test. The study was designed with 80% power to detect a 25% increase in median survival with erlotinib plus chemotherapy versus chemotherapy alone[33] (from 9.1 to 11.375 months; HR, 0.8). This required enrollment of 1,116 patients.

Secondary efficacy parameters were analyzed using a two-sided log-rank test (TTP and time to symptomatic progression) and a χ^2 test (objective RR), whereas Kaplan-Meier survival analysis was used to estimate medians and 95% CIs (duration of survival, TTP, and duration of response). PK data were analyzed by noncompartmental methods using WinNonLin version 4.0.1 (Scientific Consultant, Apex, NC; Pharsight Corp, Mountain View, CA). Safety analyses were performed for all patients who received at least one dose of trial medication and had at least one safety follow-up visit.

RESULTS

Patients

A total of 1,172 patients (586 per treatment arm) were randomly assigned between November 2001 and September 2002. The number of treated patients in each arm was 580 (erlotinib) and 579 (placebo). Baseline demographics and disease characteristics were well balanced between treatment arms (Table 1).

Efficacy

OS was similar for the erlotinib and placebo arms (Fig 2). Median OS was 43 and 44.1 weeks, respectively (HR, 1.06; 95% CI, 0.90 to 1.23; $P = .49$). One-year survival rates were 41% and 42%, respectively. Median overall TTP was 23.7 and 24.6 weeks, respectively (HR, 0.98; 95% CI, 0.86 to 1.11; $P = .74$).

The proportion of patients with objective responses (complete and partial) was also similar (31.5% *v* 29.9% for erlotinib and placebo, respectively). More than 50% of patients in both groups had a partial response or stable disease. The duration of response was significantly greater for erlotinib than for placebo (median, 25.4 *v* 23.9 weeks, respectively; HR, 0.77; 95% CI, 0.60 to 1.00; $P = .045$; Fig 3). The median time to symptomatic progression (QoL) was similar between treatment groups (68 *v* 76 days; n = 1,054).

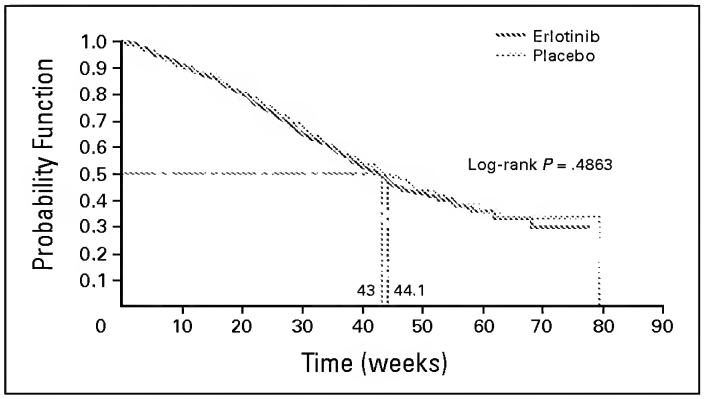

Fig 2. Kaplan-Meier estimates of overall survival (full analysis set); log-rank test.

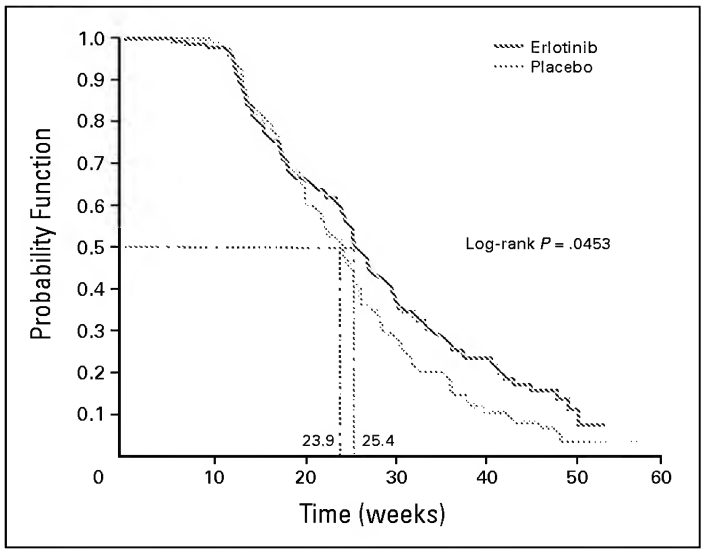

Fig 3. Kaplan-Meier estimates of duration of response to treatment for measurable disease population; log-rank test.

Exploratory subgroup analyses of OS, TTP, and tumor response by baseline characteristics (as shown in Table 1) showed no better or worse outcomes in any subgroup than overall. Median survival was 227 days in patients without rash, versus 323 days (grade 1 rash), 313 days (grade 2), and 387 days (grade 3; $P = .0001$, log-rank test) in patients with rash.

Smoking history was collected retrospectively, and was available for a small number of patients. Median survival in never-smokers (n = 10) was 11.4 months with placebo, but was not reached with erlotinib (n = 8). Median progression-free survival was longer with erlotinib (7.9 months) than with placebo (5.4 months; HR, 0.195; $P = .02$).

EGFR expression was analyzed in 376 tumor samples; the final score was available for 375 samples. The distribution of immunohistochemistry scores was similar in the placebo and erlotinib arms (0+, 30% and 33%; 1+, 9% and 9%; 2+, 19% and 20%; 3+, 32% and 40% for placebo and erlotinib arms, respectively). EGFR expression was not correlated with response or survival.

Duration of Therapy, Exposure, and PK Parameters

Eighty-four percent of patients in both treatment arms had withdrawn from the study at the time of final analyses. Reasons included AEs (126 erlotinib *v* 98 placebo), death (93 erlotinib *v* 100 placebo), insufficient therapeutic response (141 erlotinib *v* 164 placebo), refusal of treatment (75 erlotinib *v* 57 placebo), protocol violation (three erlotinib *v* seven placebo), and lost to follow-up (nine erlotinib *v* six placebo).

Exposure was similar between the treatment groups, although mean and median cumulative exposures were slightly lower for erlotinib (23.2 and 18.9 g, respectively) than for placebo (26.8 and 24.9 g). The mean daily dose of erlotinib (134.7 mg/d) was slightly lower than that for placebo (145.2 mg/d). More than 50% of patients in both arms received five or six cycles of chemotherapy; there were only marginal differences in cumulative exposure.

Blood samples from 12 patients in the initial safety cohort showed no difference in PK parameters between erlotinib administered alone (day −1) or with cisplatin and gemcitabine (cycle 1, day 1;

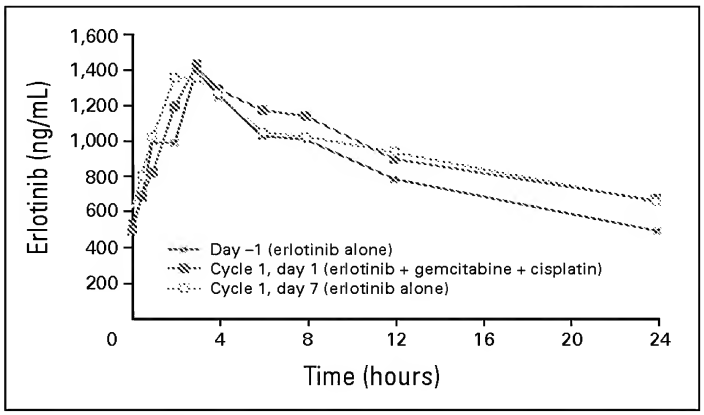

Fig 4. Mean erlotinib concentrations versus time.

Fig 4). Furthermore, erlotinib concentrations after daily dosing (cycle 1, day 7) were similar to those on days −1 and 1 of cycle 1, indicating no effect of repeated dosing with cisplatin and gemcitabine on the PK of erlotinib. PK parameters for cisplatin and gemcitabine were unaffected by coadministration of erlotinib (data not shown).

Second-Line Therapy

Of the 348 patients (179 erlotinib, 169 placebo) who received additional chemotherapy (mostly second-line therapy), the most frequently prescribed treatment was docetaxel (67 erlotinib, 88 placebo); the next most used were carboplatin and vinorelbine.

Median survival time (with second-line treatment censored) was 44.9 weeks (erlotinib) and 48.7 weeks (placebo; HR, 1.08), whereas median survival regardless of second-line therapy was 43 and 44.1 weeks for the erlotinib and placebo groups, respectively (HR, 1.06).

Table 2. Summary of Grade 3/4 Adverse Events Occurring in > 2% of Patients

	Placebo (n = 579)		Erlotinib (n = 580)	
Adverse Event	No. of Patients	%	No. of Patients	%
Hematologic				
Neutropenia	118	20	107	18
Anemia NOS	73	13	102	18
Thrombocytopenia	80	14	90	16
Leucopenia NOS	59	10	54	9
Nonhematologic				
Rash	4	< 1	60	10
Dyspnea	51	9	40	7
Vomiting NOS	43	7	39	7
Nausea	32	6	32	6
Diarrhea NOS*	5	< 1	35	6
Fatigue	30	5	31	5
Asthenia	21	4	21	4
Anorexia	12	2	20	3
Pulmonary embolism	11	2	19	3
Weight decrease	7	1	18	3
Pneumonia	13	2	16	3

NOTE. Data are for the safety population.
Abbreviation: NOS, not otherwise specified.
*Incidence of all grades of diarrhea: placebo, 17%; erlotinib, 40%.

Safety and Tolerability

Table 2 summarizes the grade 3/4 AEs recorded in more than 2% of patients. The incidence of AEs was similar between treatment arms, except for an increased incidence of rash and diarrhea with erlotinib. These are common AEs associated with EGFR TK inhibition. Anemia was also more frequent in the erlotinib group. Most other AEs were attributable to disease progression and chemotherapy-related toxicity. For AEs occurring between ≥ 5% and less than 10% of patients (data not shown), incidence was similar between treatment groups, except for severe renal impairment/failure (erlotinib 5% *v* placebo 1%).

The combination of erlotinib, cisplatin, and gemcitabine was generally well tolerated and did not produce substantial additional toxicity. Overall, a slightly higher proportion of AEs in the erlotinib group was considered treatment related (63.3% *v* 56.9%). The incidence of grade 3/4 AEs for erlotinib plus chemotherapy (77%) was only marginally higher than for chemotherapy alone (72%). Similarly, only slightly greater incidence of serious AEs was seen with erlotinib plus chemotherapy (53%) than chemotherapy alone (47%), and slightly more patients withdrew from treatment because of AEs (22% *v* 17%), mainly due to skin disorders (5% *v* < 1%).

Two occurrences of interstitial lung disease (ILD) were recorded in the placebo group, but were not serious. One patient receiving erlotinib died as a result of atypical primary pneumonia, which was considered remotely related to treatment, and postmortem examination revealed ILD.

During the trial, 680 patients died: 343 (59%) in the erlotinib arm and 337 (58%) in the placebo arm. Most deaths were attributable to disease progression (277 and 268, respectively). A similar number of patients died as a result of an AE in each treatment arm (64 *v* 68, respectively). Of these AEs, almost all were considered unrelated to study medication. Nine AEs leading to death were probably related to treatment (eight erlotinib, one placebo). These were renal failure (n = 2), neutropenia/febrile neutropenia/neutropenic sepsis (n = 3), dyspnea (n = 1), cardiovascular disorder (n = 1), and myocardial infarction (n = 1; placebo).

DISCUSSION

This study examined the efficacy and safety of erlotinib combined with cisplatin and gemcitabine for first-line treatment of advanced NSCLC. Overall, the erlotinib combination did not show any survival benefit compared with chemotherapy alone; median OS was 43 weeks for erlotinib plus chemotherapy and 44.1 weeks for placebo plus chemotherapy. There were no significant differences in TTP, RR, or time to symptomatic progression (QoL) between the two groups. Similar results were reported from a phase III trial of erlotinib plus carboplatin and paclitaxel (TRIBUTE [Tarceva responses in conjunction with paclitaxel and carboplatin]), in advanced NSCLC.[37] These results are also consistent with phase III trials of the EGFR TKI gefitinib combined with platinum-based chemotherapy.[38,39]

Most AEs seen during the study were attributable to disease progression or chemotherapy. Diarrhea and skin toxicity were the most common AEs in the erlotinib group. Erlotinib plus chemotherapy was associated with a small increase in serious AEs and treatment-related deaths. An unexpected finding was an increased incidence in renal failure with the erlotinib combination (5% *v* < 1%). This increase probably was due to insufficient hydration

after erlotinib-related diarrhea, thus exacerbating the known renal toxicity of cisplatin.[40] No increase in renal failure was observed with erlotinib plus carboplatin (a less renal-toxic drug) and paclitaxel.[37]

A high incidence of ILD was reported in NSCLC patients treated with gefitinib in Japan.[41,42] In the current study, two of the three patients with ILD had received placebo, indicating that ILD can be related to disease progression rather than EGFR TK inhibition.

The findings of the current study are in contrast with preclinical and other clinical studies with erlotinib. In mice bearing human NSCLC xenografts, coadministration of erlotinib with cisplatin or gemcitabine produced additive or synergistic antitumor activity.[31] In patients with advanced pancreatic cancer, erlotinib plus gemcitabine prolonged survival significantly. This was the first trial to show an improvement in survival in pancreatic cancer by adding a second drug to gemcitabine, and led to approval of erlotinib for the treatment of pancreatic cancer in the United States.[43] Furthermore, in a phase III trial (BR.21), erlotinib monotherapy significantly improved survival (42.5%) compared with placebo (6.7 *v* 4.7 months; HR, 0.70; $P < .001$) in 731 patients with previously treated, advanced NSCLC,[29] leading to approval in a number of countries (including the United States and European Union) as second-/third-line monotherapy for advanced NSCLC. Conversely, the lack of benefit seen here is analogous to other findings in advanced NSCLC, in which the addition of a third cytotoxic drug provided minimal survival benefit compared with newer two-drug combinations,[7,44-46] possibly due to greater toxicity with triplets.

The reasons for the lack of benefit from erlotinib plus chemotherapy are unknown, but the PK results indicate that erlotinib had no effect on plasma levels of either cisplatin or gemcitabine, or vice versa. Thus, a negative PK interaction between erlotinib and chemotherapy is unlikely. An analysis of the BR.21 study indicated that smoking reduces erlotinib exposure due to induction of cytochrome P450IA enzymes.[47] This may help to explain the apparent survival benefit among never-smokers in the current study, but due to the small numbers of patients involved, this is only supposition. Among never-smokers in the TRIBUTE study (n = 72), addition of erlotinib led to a more than two-fold improvement in median survival versus chemotherapy alone. TTP was also prolonged; the RR was 30% for erlotinib plus chemotherapy versus 11% for chemotherapy alone.[37]

There was no clear association between EGFR expression and response, corroborating previous findings with erlotinib and other EGFR TKIs in NSCLC.[27,37,48,49] However, the methods used may have been insufficiently sensitive to detect this effect; chemotherapy may be another confounding factor. EGFR TK mutations seem to be associated with tumor response to another EGFR TKI, gefitinib, in NSCLC.[50,51] However, there has been no prospective correlation between the presence of mutations and OS. In a small retrospective study, mutations were found in five of seven tumors from NSCLC patients sensitive to erlotinib and were found more commonly in never-smokers. None were found in nonresponding tumors.[52] Tumor samples from TALENT currently are being analyzed for mutations; the results will be published separately.[53]

The lack of an additive effect with erlotinib and chemotherapy may relate to a mechanistic interaction. Erlotinib and gemcitabine/cisplatin have different mechanisms of action (cytostatic and cytotoxic, respectively). The antiproliferative effects of erlotinib, arising from cell-cycle arrest,[22] may render tumor cells less sensitive to cytotoxic agents, as suggested by recent preclinical studies of combinations of EGFR TKIs with chemotherapy.[54,55] Erlotinib also has proapoptotic effects[22] that could enhance the antitumor effects of chemotherapy, and this may be more prominent in tumors with mutant EGFR than those with wild-type receptors.[56] This may partly explain the benefit seen in never-smoking patients, who are more likely to have mutations. The mechanisms by which erlotinib may achieve antitumor activity when added to chemotherapy are unclear, as shown by the improvement in survival with erlotinib plus gemcitabine in pancreatic cancer. Preclinical data suggest that alternative dosing schedules, such as sequential or pulse dosing of erlotinib, may prove more effective than concurrent administration.[54] In the current trial, patients treated with erlotinib for more than 150 days showed increased response duration compared with placebo, suggesting that treatment with erlotinib after chemotherapy may be beneficial; maintenance therapy with erlotinib is the subject of an ongoing investigation.

As reported in a phase II NSCLC trial,[27] a relationship between treatment-emergent rash and survival was observed, but the relevance is unclear. Rash is also common with other compounds targeting EGFR.

In conclusion, TALENT did not demonstrate improved efficacy from addition of erlotinib to cisplatin and gemcitabine in patients with previously untreated, advanced NSCLC. Long survival times were seen in a small number of patients who had never smoked. The triplet combination was well tolerated, confirming the good tolerability of erlotinib. Alternative dosing schedules are being investigated, to integrate effectively erlotinib with chemotherapy in advanced NSCLC, and analyses to identify patients most likely to benefit from erlotinib are ongoing.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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ORIGINAL REPORT

TRIBUTE: A Phase III Trial of Erlotinib Hydrochloride (OSI-774) Combined With Carboplatin and Paclitaxel Chemotherapy in Advanced Non–Small-Cell Lung Cancer

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
Erlotinib is a potent reversible HER1/epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor with single-agent activity in patients with non–small-cell lung cancer (NSCLC). Erlotinib was combined with chemotherapy to determine if it could improve the outcome of patients with NSCLC.

Patients and Methods
TRIBUTE randomly assigned patients with good performance status and previously untreated advanced (stage IIIB/IV) NSCLC to erlotinib 150 mg/d or placebo combined with up to six cycles of carboplatin and paclitaxel, followed by maintenance monotherapy with erlotinib. Random assignment was stratified by stage, weight loss in the previous 6 months, measurable disease, and treatment center. The primary end point was overall survival (OS). Secondary end points included time to progression (TTP), objective response (OR), and duration of response.

Results
There were 1,059 assessable patients (526 erlotinib; 533 placebo). Median survival for patients treated with erlotinib was 10.6 *v* 10.5 months for placebo (hazard ratio, 0.99; 95% CI, 0.86 to 1.16; $P = .95$). There was no difference in OR or median TTP. Patients who reported never smoking (72 erlotinib; 44 placebo) experienced improved OS in the erlotinib arm (22.5 *v* 10.1 months for placebo), though no other prespecified factors showed an advantage in OS with erlotinib. Erlotinib and placebo arms were equivalent in adverse events (except rash and diarrhea).

Conclusion
Erlotinib with concurrent carboplatin and paclitaxel did not confer a survival advantage over carboplatin and paclitaxel alone in patients with previously untreated advanced NSCLC. Never smokers treated with erlotinib and chemotherapy seemed to experience an improvement in survival and will undergo further investigation in future randomized trials.

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INTRODUCTION

Lung cancer is the most common cause of cancer deaths worldwide, and the development of more effective therapy remains challenging.[1] The development of agents that target the epidermal growth factor receptor (EGFR) signal transduction pathways have provided a class of novel targeted therapeutic agents.[2]

Erlotinib (Tarceva; Genentech Inc, San Francisco, CA) is a potent reversible HER1/EGFR tyrosine kinase inhibitor (EGFR-TKI). This is a report of a phase III trial that

evaluated whether concurrent administration of erlotinib with standard chemotherapy could enhance survival in chemotherapy-naïve patients with advanced or metastatic non–small-cell lung cancer (NSCLC).

Erlotinib has been evaluated in a number of phase I and II studies as a single agent.[3,4] In a phase II trial, 57 patients with advanced or recurrent NSCLC who had previously received platinum-based chemotherapy received erlotinib 150 mg/d as a single agent.[5] In this study, patients had measurable tumors that expressed a low level of EGFR by immunohistochemical (IHC) analysis. The objective response rate of 12.3% (95% CI, 5.1% to 23.7%) and median survival of 8.5 months were comparable to results noted for docetaxel, pemetrexed, or gefitinib in refractory NSCLC.[6,7] The most common adverse events with erlotinib consisted of mild/moderate rash and diarrhea.

Preclinical evaluations of erlotinib in athymic nude mice bearing tumor xenografts in HN5 head and neck and A431 epidermoid carcinoma cell lines established the effective dose for 50% inhibition of growth. Further evaluation in H460a and A549 NSCLC, and HN5 tumor models at the 50% inhibition of growth in combination with chemotherapy were conducted. No antagonism was detected with any of the chemotherapy agents evaluated, including paclitaxel and cisplatin. Additive effects were observed with some cytotoxic combinations of erlotinib, including paclitaxel and cisplatin.[8,9]

On the basis of phase II results and the therapeutic advantage demonstrated preclinically with erlotinib with platinum-based and taxane chemotherapy, a phase III trial was conducted using erlotinib in combination with paclitaxel and carboplatin.

This trial, designated TRIBUTE (Tarceva responses in conjunction with paclitaxel and carboplatin), was a multicenter (United States), randomized, placebo-controlled trial of paclitaxel and carboplatin with or without erlotinib in chemotherapy-naïve patients with advanced NSCLC. The primary objective was to determine if the concurrent addition of erlotinib to paclitaxel plus carboplatin could prolong overall survival. Secondary objectives included improvement in time to progression (TTP), objective response rate, and safety.

PATIENTS AND METHODS

Eligibility Criteria

Inclusion required histologically documented stage IIIB or stage IV NSCLC; age ≥ 18 years; and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Exclusion criteria included prior systemic chemotherapy for NSCLC; symptomatic or untreated brain metastases, prior exposure to agents directed at the HER axis; unstable systemic disease that would potentially preclude chemotherapy treatment with or without erlotinib; inadequate hematologic (granulocytes ≤ 1.5/mL), renal (creatinine > 1.5× upper limit of normal [ULN]), or hepatic function (liver function tests > 2.5× ULN). EGFR protein expression determination (by IHC methodology) was not an a priori condition for enrollment.

All patients provided informed consent, and approval was obtained from the ethics committee at each center. The study followed the Declaration of Helsinki and good clinical practice guidelines.[10]

Trial Design

Patients were randomly assigned to receive either daily oral erlotinib or placebo concurrently with chemotherapy (Fig 1). Randomization was stratified by disease stage (IIIB; IV), weight loss during the previous 6 months (≤ 5%; > 5%), tumor measurability (measurable; nonmeasurable), and treatment center. Patients received a maximum of six cycles of paclitaxel (200 mg/m^2) followed by carboplatin (to achieve an area under concentration/time curve of 6 mg/mL · min) every 3 weeks in the absence of disease progression.

To evaluate the safety of erlotinib plus carboplatin/paclitaxel and to establish the starting erlotinib dose in this setting, the first 50 patients started therapy at 100 mg in the week before and during the first cycle of concurrent chemotherapy. If the study drug was tolerated, dose was escalated to 150 mg daily on day 15 of the first cycle.

Based on an acceptable safety profile, an independent Dose Selection Committee determined that a starting dose of 150 mg was tolerable. Following dose selection, approximately 1,000 patients were enrolled using this starting dose. Recommendations were provided for management of severe or intolerable rash or diarrhea (including guidelines for dose-reduction or interruption of study drug).

Due to the fact that there was no prior experience with the combination of erlotinib with carboplatin and paclitaxel in NSCLC, the first 400 patients were intensely monitored for safety to further assess for possible interaction between the chemotherapy specified for the study and concurrent administration of erlotinib. All adverse events were collected regardless of causality or relationship to study drugs. For the remaining 650 patients, collection of safety information was limited to serious adverse events, and all adverse events leading to study-drug or chemotherapy-dose interruption, reduction, or discontinuation. All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 6.0. Severity was determined using the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0.

Twenty-four patients (12 in each treatment arm) enrolled at the M.D. Anderson Cancer Center underwent pharmacokinetic

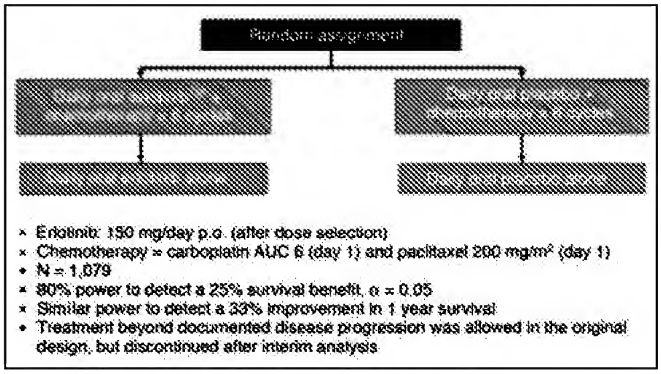

Fig 1. Study schema.

sampling for erlotinib, paclitaxel, and carboplatin. These patients were enrolled after the final erlotinib dose had been selected. Sampling for OSI-774 (and its major metabolite OSI-420) occurred within 2 days of cycle 2, at 3 and 4 hours post-erlotinib. The sample schedule for day 1 of cycle 2 for erlotinib, paclitaxel, and carboplatin is presented in Table 1. Blood samples for OSI-774 and carboplatin were drawn into 2-mL heparinized tubes, while blood for paclitaxel assay was drawn into a 2-mL K-EDTA tube. All samples were centrifuged within 30 minutes of sample collection, for 10 minutes at 4°C at 3,000 × *g*. Plasma was extracted, frozen, and stored at ≤ −80°C.

Statistical Analysis

The primary end point was survival for the intent-to-treat population. For all patients alive at the time of the statistical analysis, survival was censored at the date of last contact. Secondary end points included TTP and response rate.

The study was designed to have 80% power for a two-sided hypothesis test that erlotinib with carboplatin/paclitaxel increased median survival by 25% relative to survival reported for carboplatin/paclitaxel alone within a randomized trial of four chemotherapy regimens. A median survival of approximately 8 months was reported in ECOG and Southwest Oncology Group trials with carboplatin/paclitaxel in a similar population.[11,12] A 25% improvement in survival associated with the combination of erlotinib with this regimen would result in a median survival of 10.13 months (a hazard ratio of 0.80). Based on these assumptions, 642 events were required corresponding to enrollment of 1,050 patients. This sample size was also sufficient to detect a 33% improvement in 1-year survival, with similar statistical power.

Table 1. Intensive PK Population: Sample Schedule

Cycle 2/Nominal Time (hours)	OSI-774 and OSI-420	Paclitaxel	Carboplatin
Day 1 administer erlotinib/ begin paclitaxel			
0			
Post-erlotinib			
0.25	X		
0.50	X		
1	X	X	
2	X	X	
Draw 5 minutes before end of paclitaxel; begin carboplatin			
3	X	X	
3.25		X	
Draw 5 minutes before end of carboplatin			
3.5		X	X
3.75		X	X
4	X	X	X
5		X	X
6	X	X	X
8	X	X	X
12	X	X	X
Day 2 prior to erlotinib			
24	X	X	X
Day 3 prior to erlotinib			
48	X	X	
Day 8 prior to erlotinib			
168	X		

Survival, TTP, and objective response rate were summarized by predefined categories including age, sex, ECOG performance status, weight loss during the previous 6 months, disease stage, smoking history, and selected markers on the EGFR pathway. Smoking history was collected prospectively as a data element within the screening case report forms. Patients were asked whether they had a prior smoking history, and, if so, the number of prior pack years. No minimum prior exposure (eg, ≤ 100 cigarettes) was used to define never smokers for this study.

Based on emerging results regarding efficacy in never smokers treated with EGFR tyrosine kinase inhibitors, the statistical analytic plan for the study was revised before unblinding to include such an analysis in this trial.

The Cox proportional hazards model was used to estimate the effect of risk factors on survival and TTP and to evaluate any modifications of treatment effect. To evaluate the effects of baseline characteristics on objective response rates and to assess modifications of treatment effect, a logistic regression model was applied.

An independent Data Monitoring Committee (DMC) reviewed safety on a quarterly basis and performed an interim analysis of efficacy and safety (321 deaths), in order to potentially terminate the study if the DMC had safety concerns or if robust efficacy was demonstrated.

Assessments

Tumor response was determined by Response Evaluation Criteria in Solid Tumors (RECIST).[13] Tumor assessments were performed on day 21 of chemotherapy cycles 2, 4, and 6, and every 8 weeks following completion of chemotherapy. Time to symptomatic deterioration was assessed via the Lung Cancer Symptom Scale at these intervals. EGFR expression was determined retrospectively via IHC staining analysis on unstained slides, if available.[14] Positive EGFR expression was indicated by weak to strong membranous staining in 10% or more tumor cells. Safety was evaluated by analyzing adverse events and laboratory tests.

RESULTS

Patients

Between July 18, 2001, and August 19, 2002, 1,079 patients were randomly assigned: 539 patients to erlotinib and 540 patients to placebo. Demographic and disease characteristics were balanced between the two treatment arms (Table 2). The majority of patients in both treatment arms had stage IV disease, with ≤ 5% weight loss in the previous 6 months.

Efficacy

Median survival was 10.6 months in the erlotinib arm versus 10.5 months in the placebo arm (hazard ratio, 0.995; 95% CI, 0.86 to 1.16; $P = .95$; Fig 2A). TTP was 5.1 months for erlotinib and 4.9 months for placebo ($P = .36$; Fig 2B).

The objective response rate (complete and partial) was similar between the erlotinib and placebo arms (21.5% *v* 19.3%, respectively; $P = .36$) and were partial responses in both arms.

Subset analyses failed to demonstrate any significant improvement in survival by age, sex, race, cancer stage,

Table 2. Patient Characteristics

	Placebo (n = 540*)		Erlotinib (n = 539)	
	No.	%	No.	%
Sex	n = 539		n = 539	
Female	207	38.4	217	40.3
Male	332	61.6	322	59.7
Age, years	n = 539		n = 539	
Mean	62.6		62.7	
Standard deviation	10.1		10.5	
Median	63		63	
Range	26 to 84		24 to 84	
Cancer stage	n = 539		n = 539	
IIIB	96	17.8	84	15.6
IV	443	82.2	455	84.4
ECOG performance status	n = 538		n = 539	
0	195	36.2	186	34.5
1	342	63.6	353	65.5
2	1	0.2	0	0
Weight loss > 5% within 6 months	n = 537		n = 539	
No	368	68.3	374	69.4
Yes	169	31.5	165	30.6
Tumor type	n = 540		n = 539	
Measurable	504	93.3	506	93.9
Nonmeasurable	36	6.7	33	6.1
Histology	n = 539		n = 539	
Adenocarcinoma	331	61.4	323	59.9
Large-cell carcinoma	56	10.4	43	8.0
Squamous cell carcinoma	87	16.1	98	18.2
Other	65	12.1	75	13.9
Race/ethnicity	n = 539		n = 539	
White	482	89.4	452	83.9
Black	33	6.1	37	6.9
Asian/Pacific Islander	13	2.4	21	3.9
Hispanic	7	1.3	25	4.6
American Indian or Alaskan Native	2	0.4	1	0.2
Other	2	0.4	3	0.6
Prior smoking history	n = 539		n = 539	
Never	44	8.2	72	13.4
Current	106	19.7	100	18.6
Previous	389	72.2	367	68.1

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*One patient was enrolled, but found to be ineligible prior to any study treatment or assessments. This patient was included in the intent-to-treat analysis of survival only.

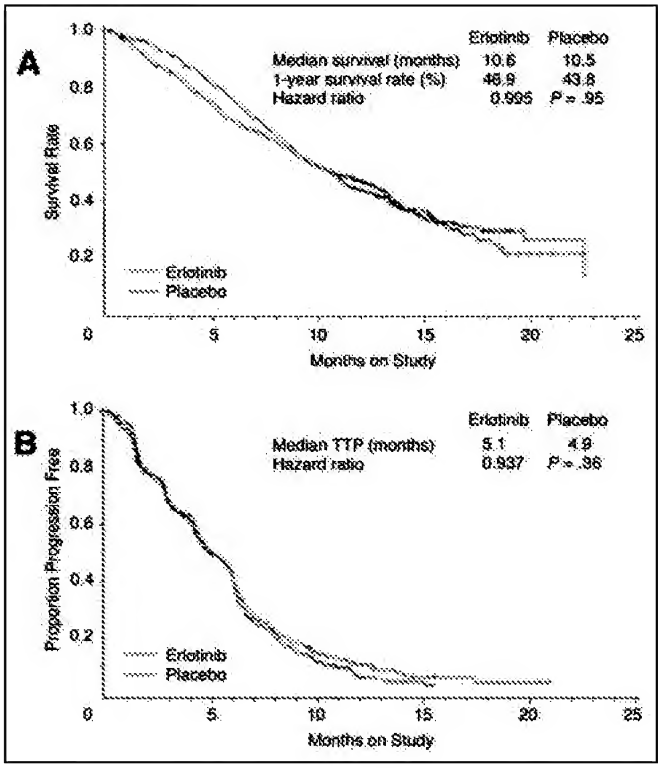

Fig 2. Survival (A) and time to progression (B) intent-to-treat population. TTP, time to progression.

ECOG status, prior weight loss, histology, previous cancer-related surgery, or EGFR expression. There was no correlation between the level of EGFR expression (as assessed by IHC staining analysis using the DakoCytomation PharmDx test kit; DakoCytomation, Carpinteria, CA) and clinical outcome. Unstained slides were available for 445 of the 1,079 patients enrolled on the study. Of these, 344 were assessable for analysis (180 erlotinib, 164 placebo). The hazard ratio for EGFR-positive histology (93 erlotinib, 74 placebo) was 1.00 (95% CI, 0.69 to 1.45) versus a hazard ratio for EGFR-negative histology (87 erlotinib, 90 placebo) of 1.02 (95% CI, 0.71 to 1.46).

Analysis for the newly identified somatic mutations in the EGFR kinase domain was performed on 228 assessable samples of diagnostic tissue and will be reported in detail elsewhere.[15,16]

One prespecified subset had a difference in outcome. Patients who reported that they had never smoked experienced substantial prolongation in survival with erlotinib treatment: 22.5 months (n = 72) versus 10.1 months in the placebo arm (n = 44; hazard ratio of 0.49; 95% CI, 0.28 to 0.85; Fig 3), which was independent of tumor histology. Median overall survival of never smokers treated with chemotherapy alone was similar to that of former or current smokers in the same treatment arm (10 months). These results for never smokers contrasted sharply with the outcome for current (8.4 months erlotinib; 9.1 months placebo) and previous smokers (10.0 months erlotinib; 10.9 months placebo).

The median TTP in never smokers was 6.0 months in the erlotinib arm versus 4.3 months for placebo (hazard ratio, 0.50; 95% CI, 0.31 to 0.80). The response rate of never smokers receiving erlotinib plus carboplatin/paclitaxel was significantly higher than that of those receiving carboplatin/paclitaxel alone (21 [30%] of 69; 95% CI, 20% to 43% *v* five [11%] of 44; 95% CI, 4% to 25%; $P = .02$). The never-smoker subset tended to be younger (58 *v* 64 years), female (60% *v* 37%), and to have adenocarcinoma (82% *v* 58%) in comparison to prior/current smokers.

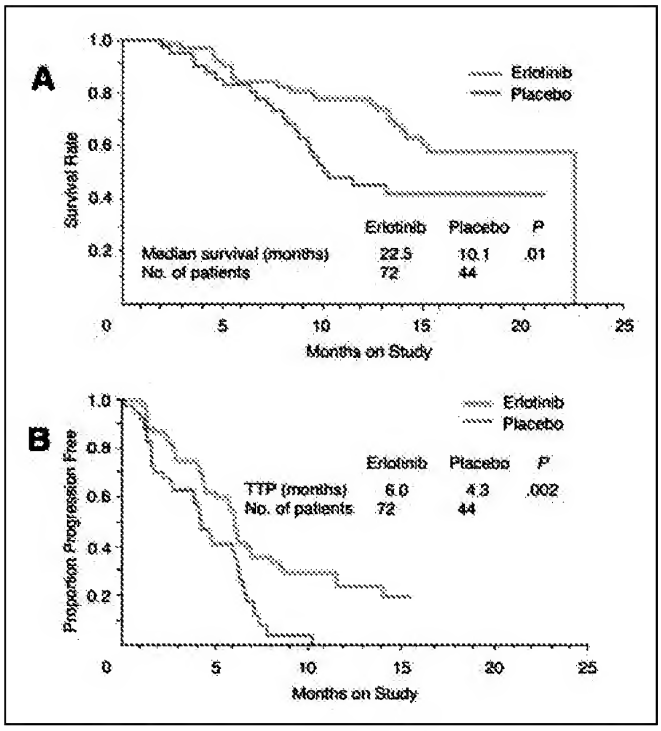

Fig 3. Survival (A) and time to progression (B) for never smokers.

An exploratory analysis of patients who survived beyond chemotherapy and received study drug as monotherapy thereafter showed an improvement in survival in the erlotinib arm that suggested a maintenance effect.

In the 861 patients who survived beyond 4 months (erlotinib 408; placebo 453), median survival with erlotinib was 13.6 *v* 12.2 months ($P = .04$). In the 740 patients who survived beyond 6 months (erlotinib 348; placebo 392), median survival with erlotinib was 15.4 *v* 13.8 months for placebo ($P = .007$).

Duration of Therapy, Dose Adherence, Dose Intensity, and Exposure

The median duration on study drug was 4.6 months with erlotinib and 5.3 months with placebo. There were more dose interruptions (because of compliance or toxicity) and reductions with erlotinib versus placebo (250 *v* 190 interruptions and 135 *v* 17 reductions, respectively). Mean total dose of study drug per patient was lower in the erlotinib arm versus in the placebo arm (24.0 g *v* 26.5 g, respectively; $P = .035$); this was also true for the mean daily dose (137.8 mg/d *v* 146.8 mg/d, respectively; $P < .0001$). Overall, 14 patients (10 erlotinib, four placebo) were unblinded early because a potential investigational new drug safety report was filed.

Exposure to chemotherapy was similar between the two treatment arms. The median number of cycles of carboplatin and paclitaxel was five for both arms ($P = .246$), whereas respective mean doses per cycle for carboplatin (619.9 mg for erlotinib 635.0 mg for placebo; $P = .1$) and paclitaxel (358.4 for erlotinib; 362.8 mg for placebo; $P = .2$) were also similar.

Carboplatin and paclitaxel sampling for pharmacokinetic analysis was performed in 21 patients. Overall, exposure to carboplatin and paclitaxel was similar between erlotinib and placebo-treated patients. Erlotinib exposure was similar to historical data from phase I and II trials.[3,5,17] Detailed results will be reported elsewhere.

Results of assessment for time to symptomatic progression as determined by assessment of lung cancer symptom scores will be presented elsewhere.

Safety and Tolerability

Adverse events in the erlotinib arm were similar in incidence and severity to those of the placebo arm, with the exception of an increased incidence of rash and diarrhea, which are known to be associated with EGFR tyrosine kinase inhibition (Table 3).

The erlotinib arm had a higher incidence of study drug–related serious adverse events relative to the placebo arm (8.6% erlotinib; 2.4% placebo). The most common events included diarrhea (3.8% erlotinib; 1.1% placebo) and rash (dermatitis acneiform; 0.8% erlotinib; 0 placebo). The rate of interstitial lung disease (ILD) was estimated by inclusion of a set of 24 preferred coding terms that have been associated with such events, regardless of causality or possible confounders. There were five severe ILD-like events in the erlotinib arm (1.0%), versus one event in the placebo arm (0.2%). All ILD-like events were fatal.

A total of 662 treated patients died before the data cutoff: 322 (61.2%) in the erlotinib arm and 340 (63.8%) in the placebo arm. The majority of the deaths in both arms were attributed to disease progression by investigators (275 erlotinib; 318 placebo).

Forty-eight deaths were attributed to an adverse event: 33 (10.2%) of 322 deaths in the erlotinib arm and 15 (4.4%) of 340 deaths in the placebo arm. The majority of the imbalance was due to infection (seven erlotinib; one placebo) and GI events (four erlotinib; one placebo).

With respect to infectious events leading to death, pneumonias accounted for six events (five erlotinib, one placebo). All such events occurred during concomitant administration of chemotherapy and study drug. None of the pneumonias leading to death were assessed as related to study drug by the respective investigators (events were related to "disease under study"/protocol-specified chemotherapy). The two remaining infectious events leading to death in the erlotinib arm were neutropenic sepsis (occurring after the first cycle of chemotherapy; assessed as related to erlotinib and protocol-specified chemotherapy) and septic shock (occurring on the fifth day of study; assessed by the investigator as related to the disease under study).

Table 3. Common Adverse Events (intensive safety population)

	% of Patients*					
	Erlotinib (n = 209)			Placebo (n = 208)		
	All	CTC Grade 3†	CTC Grade 4	All	CTC Grade 3	CTC Grade 4
Hematologic						
Anemia	51.7	6.2	1.4	41.8	5.8	0.5
Neutropenia	34.9	12.0	10.0	33.2	11.5	11.1
Thrombocytopenia	18.2	5.7	1.9	15.9	4.3	0.5
Leukopenia NOS	12.4	4.3	0.0	6.7	2.9	0.5
Febrile neutropenia	4.3	1.4	1.4	1.9	1.4	0.0
Nonhematologic						
Diarrhea NOS	67.9	12.4	0.0	38.5	4.3	0.5
Rash NOS	61.7	7.2	0.0	27.9	1.0	0.0
Nausea	61.2	3.8	0.0	59.1	5.8	0.0
Fatigue	53.6	5.3	0.5	56.3	6.3	0.0
Alopecia	49.8	0.5	0.0	56.7	0.0	0.0
Vomitting NOS	35.4	4.8	0.0	36.1	4.3	0.5
Arthralgia	34.4	2.9	0.0	34.6	3.8	0.0
Constipation	34.0	1.4	0.0	46.6	1.9	0.0
Cough	26.3	0.5	0.0	22.1	0.0	0.0
Dyspnea	24.9	5.7	1.4	26.0	3.8	2.4
Dermatitis acneiform	21.5	3.3	0.0	6.7	0.0	0.0
Peripheral neuropathy NOS	16.3	0.0	0.0	26.4	1.9	0.0

Abbreviations: CTC, National Cancer Institute Common Toxicity Criteria, version 2.0; NOS, not otherwise specified.
*Intensive safety population: first 400 patients enrolled; all adverse events collected regardless of severity.

All of the GI events leading to death occurred during the phase of concomitant administration of chemotherapy and study drug. Of the GI events leading to death in the erlotinib arm, there was one case of GI hemorrhage assessed as related to erlotinib and concomitant medication (ie, warfarin sodium). Another erlotinib patient experienced a GI perforation on study day 17 (after one cycle of chemotherapy) and declined surgical intervention. Diarrhea led to death in a patient with a history of diabetes mellitus who had experienced nausea, vomiting, and diarrhea since the first cycle of chemotherapy, on study day 8 (assessed as related to concurrent illness and medication). Finally, intestinal ischemia was the cause of death on study day 11 and was assessed as related to the single cycle of protocol-specified chemotherapy by the treating physician. The single GI event leading to death in the placebo cohort was perforation of a gastric ulcer after five cycles of chemotherapy (assessed as related to disease under study, and concurrent medication and illness).

Twenty-one deaths were attributed to other causes: 14 (4.3%) of 322 deaths in the erlotinib arm and seven (2.1%) of 340 in the placebo arm. Nine deaths in this category were due to unknown causes (eight erlotinib; one placebo), while eight deaths were attributed to cardiac/pulmonary arrest (five erlotinib; three placebo).

There were more early deaths (ie, during concomitant administration of chemotherapy and study drug) in the erlotinib arm. At study day 120 (the point of maximum difference between treatment arms), there were 105 deaths in erlotinib arm versus 70 in placebo. The majority of early deaths in TRIBUTE were attributed to progression of underlying lung cancer (78% erlotinib, 87% placebo). This effect was also evident in the phase III trial of gefitinib with concurrent administration of the same chemotherapy regimen (INTACT-2).[18]

DISCUSSION

This randomized, placebo-controlled trial examined the efficacy and safety of erlotinib in combination with paclitaxel and carboplatin for first-line therapy of advanced NSCLC in 1,079 unselected patients. There was no improvement in survival, TTP, or response rate compared with chemotherapy given alone. These clinical results contrast with preclinical studies, suggesting additive effects of combining erlotinib and paclitaxel and a platinum.

These results are consistent with previous reports in which paclitaxel and carboplatin were combined with an EGFR-TKI.[18] In contrast to these combination studies, erlotinib monotherapy effected a statistically significant survival advantage over placebo in 731 patients with recurrent, previously treated NSCLC. Erlotinib was associated with a 37% improvement in overall survival (log-rank hazard ratio, 0.73; 95% CI, 0.6 to 0.87; $P = .001$) and progression-free survival (hazard ratio, 0.61; 95% CI, 0.51 to 0.73; $P < .001$).[19]

Although a post hoc analysis of patients who had lived beyond concomitant administration of study drug with chemotherapy suggested a survival benefit associated with erlotinib, such results must be viewed with obvious caution. One has to consider that such patients who demonstrated a benefit in this analysis had completed chemotherapy with erlotinib. As such, use of erlotinib in a maintenance setting after first-line chemotherapy has not been proven and will need to be evaluated prospectively in a randomized trial setting to demonstrate its potential therapeutic benefit.

In light of the positive preclinical data, the lack of benefit in the first-line trial when erlotinib was combined with chemotherapy may be based on an as yet unidentified negative interaction when an EGFR-TKI is given concurrently with a platinum-based regimen and a taxane. However, the efficacy of erlotinib to carboplatin and paclitaxel in the never smoker population argues against antagonism. In addition, there was no apparent pharmacokinetic interaction between erlotinib and carboplatin and paclitaxel in this trial.

The patients enrolled in TRIBUTE were not selected based on known prognostic factors. Betensky et al presented a model for the potential effect of molecular heterogeneity in trial design.[20] If such heterogeneity were to confer a treatment benefit in a subset of patients, the overall trial could be underpowered to detect an effective therapy. Thus, one possible explanation for the negative results may be the lack of patient selection for such a factor, at least in the first-line setting. For example, the discovery of mutations in the EGFR tyrosine kinase domain in some patients may be one example of the potential to appropriately select for a subset of patients who may benefit from EGFR inhibition in the first-line setting.

Sensitivity to erlotinib or gefitinib has been strongly associated with mutations, most commonly, deletions of four to six amino acids in exon 19 or a point mutation (L858R) in exon 21. The tissue blocks from the patients participating in TRIBUTE have been studied for EGFR mutations, and this analysis will be reported in a separate publication.

The fact that never smokers who received chemotherapy plus erlotinib achieved a 120% increase in median survival as compared with the patients who received chemotherapy alone supports this hypothesis, and argues against a universally unfavorable negative interaction with chemotherapy. This finding, however, needs to be validated in an appropriately designed clinical trial.

While the observation in never smokers might be spurious, the similar demographics and balanced baseline characteristics between the two arms of this study argues against this. In addition, similar results were also observed in the recently completed trial of single-agent erlotinib in patients with refractory advanced NSCLC conducted by the National Cancer Institute of Canada (NCIC), as well as in INTACT-2 with gefitinib.[18,19] However, in the NCIC trial, a survival benefit was also observed for patients who were current/prior smokers.

Recent work by several groups has suggested that never smokers are more likely to harbor mutations than smokers in the tyrosine kinase domain of EGFR. For example, Pao et al reported such mutations in seven of 15 unselected early-stage never smokers with adenocarcinoma.[21]

The low response rate of never smokers treated with chemotherapy and placebo in this trial (11%) raises the question of whether patients who may have an increased likelihood of these mutations are less sensitive to cytotoxic chemotherapy. Unpublished, preclinical studies in which cell lines that harbor these mutations are treated with both EGFR-TKIs and cytotoxic chemotherapy are ongoing.[21A] However, the long survival observed in these patients, which is far greater than that seen in any reported phase II or III trial to date, might simultaneously suggest a favorable interaction between chemotherapy and erlotinib. In never smokers, it would be important to investigate prospectively the value of combining erlotinib with chemotherapy versus erlotinib alone.

Studies have now shown that tumors of never smokers are molecularly less complex and may confer a better prognosis for patients.[22] In some countries within the Pacific Rim, lung cancer, particularly in females, is far more common in never smokers than smokers. Thus, racial background and smoking history should be considered when designing and interpreting clinical trials in NSCLC, particularly with EGFR-TKIs.

The side effects of rash and diarrhea associated with erlotinib seemed to be characteristic of this class of drugs. In addition, the incidence of life-threatening toxicities such as ILD, which have rarely been reported with gefitinib, was likewise rarely observed with erlotinib in this trial (1.0% erlotinib; 0.2% placebo).[18] There was however, a higher rate of deaths (regardless of whether related to progression of NSCLC or toxicity) in the erlotinib arm relative to placebo associated with concomitant administration of chemotherapy (163 erlotinib, 125 placebo). This effect was not noted in the European counterpart trial with erlotinib, which specified a different chemotherapy regimen (gemcitabine and cisplatin). As noted previously, this is suggestive of a potential negative interaction between the carboplatin and paclitaxel regimen specified in this study and erlotinib.

Additional preclinical and clinical investigations are ongoing to identify whether alternative schedules and or dosing regimens might allow erlotinib to be combined with chemotherapy in patients with first-line stage IIIB/IV disease. In addition, the identity of clinical or molecular surrogates that may predict for improved outcome (ie, never smokers or somatic mutation in the kinase domain of EGFR) are still preliminary and will require further investigation in prospective, randomized trial settings.

Editor's Note

A related article on this subject will be published in the November 1, 2005, issue titled, Epidermal Growth Factor Receptor Mutations and Gene Amplification in Non–Small-Cell Lung Cancer: Molecular Analysis of the IDEAL/INTACT Gefitinib Trials; by Daphne W. Bell, Thomas J. Lynch, Sara M. Haserlat, Patricia L. Harris, Ross A. Okimoto, Brian W. Brannigan, Dennis C. Sgroi, Beth Muir, Markus J. Riemenschneider, Renee Bailey Iacona, Annetta D. Krebs, David H. Johnson, Giuseppe S. Giaccone, Roy S. Herbst, Christian Manegold, Masahiro Fukuoka, Mark G. Kris, Jose Baselga, Judith S. Ochs, and Daniel A. Haber.

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Roy S. Herbst			Genentech Inc (A)			Genentech Inc (A)		
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Appendix E

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Randomized study of pazopanib + lapatinib vs. lapatinib alone in patients with HER2- positive advanced or metastatic breast cancer.

Sub-category: Metastatic Breast Cancer
Category: Breast Cancer--Metastatic Breast Cancer
Meeting: 2008 ASCO Annual Meeting

Abstract No: 1016

Citation: *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 1016)

Author(s): D. Slamon, H. L. Gomez, F. F. Kabbinavar, O. Amit, M. Richie, L. Pendite, V. Goodman

Abstract: Background: Preclinical evidence indicates a direct molecular link between HER2 amplification and up-regulation of VEGF in HER2+ breast cancer. Concurrent over-expression of HER2 and VEGF is associated with a poorer clinical outcome than over-expression of either alone. Together these data provide the rationale for clinical translation of simultaneous blockade of both pathways. Pazopanib (P) is an oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-kit. Lapatinib (L) is an oral tyrosine kinase inhibitor of EGFR (ErbB1) and HER2 (ErbB2). This study (VEG20007) evaluates the efficacy and safety of dual pathway inhibition in patients (pts) with HER2+ adv/met breast cancer. **Methods:** Eligible pts received no prior chemotherapy or HER2-directed therapy for adv/met disease and had measurable disease per RECIST. Pts were randomized to receive P 400 mg/d + L 1,000 mg/d or L alone (1,500 mg/d) for 12 weeks. Following disease assessment at week (wk) 12, pts with an objective response could continue on study treatment following re-consent; those with stable disease could continue only where trastuzumab was unavailable. The primary endpoint was progressive disease rate (PDR) at wk 12 in HER2 FISH+ pts. A pre-specified interim analysis (IA) was performed when 62 of 140 pts reached wk 12. **Results:** 32 PL and 30 L pts were included in the IA (73% stage IV, 27% stage IIIb). Pts in the PL arm had a shorter time since initial diagnosis (227 vs. 380 days); baseline characteristics were otherwise well balanced. Efficacy data (by independent review) at wk 12 were available in 69% (PL) and 77% (L) of pts: PDR was 19% (PL) vs. 27% (L); response rate was 44% (PL) vs. 30% (L). Reduction in target lesions occurred in 73% (PL) vs. 43% (L) of pts. The most common adverse events (PL vs. L) were diarrhea (63 vs. 57%), rash (22 vs. 20%) and nausea (22 vs. 17%). AST (63 vs. 33%) and bilirubin (39 vs. 21%) increases were more common on PL. Asymptomatic decline in left ventricular ejection fraction led to discontinuation of 1 pt on PL. **Conclusions:** This is the first phase II trial to evaluate the combination of 2 oral targeted agents in first-line HER2+ adv/met breast cancer. Preliminary data demonstrate the activity and tolerability of PL. The final analysis will be presented.

Abstract Disclosures

Associated Presentation(s):

1. **Randomized study of pazopanib + lapatinib vs. lapatinib alone in patients with HER2- positive advanced or metastatic breast cancer.**
   Meeting: 2008 ASCO Annual Meeting
   Presenter: Dennis Slamon, MD, PhD
   Session: Breast Cancer — Metastatic (Oral Presentation)

Other Abstracts in this Sub-Category

1. **Molecular changes in the primary breast cancer versus the relapsed/metastatic lesion from a large population-based database and tissue microarray series.**
   Meeting: 2008 ASCO Annual Meeting Abstract No: 1000 First Author: R. MacFarlane
   Category: Breast Cancer--Metastatic Breast Cancer - Metastatic Breast Cancer
2. **Prognostic impact of discordance/concordance of triple-receptor expression between primary tumor and metastasis in patients with metastatic breast cancer.**
   Meeting: 2008 ASCO Annual Meeting Abstract No: 1001 First Author: K. Broglio
   Category: Breast Cancer--Metastatic Breast Cancer - Metastatic Breast Cancer
3. **Use of total HER2 and HER2 homodimer levels to predict response to trastuzumab.**
   Meeting: 2008 ASCO Annual Meeting Abstract No: 1002 First Author: K. Lenzel
   Category: Breast Cancer--Metastatic Breast Cancer - Metastatic Breast Cancer

More...

Abstracts by D. Slamon

1. **A multicenter, double-blind randomized phase II trial of neoadjuvant treatment with single-agent bevacizumab or placebo, followed by docetaxel, doxorubicin, and cyclophosphamide (TAC), with or without bevacizumab, in patients with stage II or stage III breast cancer.**

Meeting: 2008 ASCO Annual Meeting Abstract No: 562 First Author: S. A. Hurvitz
Category: Breast Cancer--Local-Regional and Adjuvant Therapy - Local-Regional Therapy

2. **Identification of predictive markers of response in colorectal cancer following treatment with dasatinib, an orally active tyrosine kinase inhibitor of *ABL* and *SRC*.**

   Meeting: 2008 ASCO Annual Meeting Abstract No: 14688 First Author: Z. A. Wainberg
   Category: Developmental Therapeutics: Molecular Therapeutics - Tyrosine Kinase Inhibitors

3. **Preferential pathologic complete response (pCR) by triple-negative (-) breast cancer to neoadjuvant docetaxel (T) and carboplatin (C).**

   Meeting: 2008 ASCO Annual Meeting Abstract No: 604 First Author: H. R. Chang
   Category: Breast Cancer--Local-Regional and Adjuvant Therapy - Adjuvant Therapy

More...

Presentations by D. Slamon

1. **Randomized study of pazopanib + lapatinib vs. lapatinib alone in patients with HER2- positive advanced or metastatic breast cancer.**

   Meeting: 2008 ASCO Annual Meeting
   Presenter: Dennis Slamon, MD, PhD
   Session: Breast Cancer — Metastatic (Oral Presentation)

2. **Survival analysis from two open-label non-randomized phase II trials of trastuzumab (H) combined with docetaxel (T) and platinums (C, cisplatin or carboplatin) (TCH) in women with HER2+ advanced breast cancer (ABC).**

   No presentation available
   Meeting: 2004 ASCO Annual Meeting
   Presenter: Dennis Slamon, MD, PhD
   Session: Breast Cancer (General Poster Session)

   More...

Randomized Phase II Study of Pazopanib + Lapatinib vs Lapatinib Alone in Patients With HER2-Advanced or Metastatic Breast Cancer

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O Amit,[3] M Richie,[3] L Pandite,[3] V Goodman[3]

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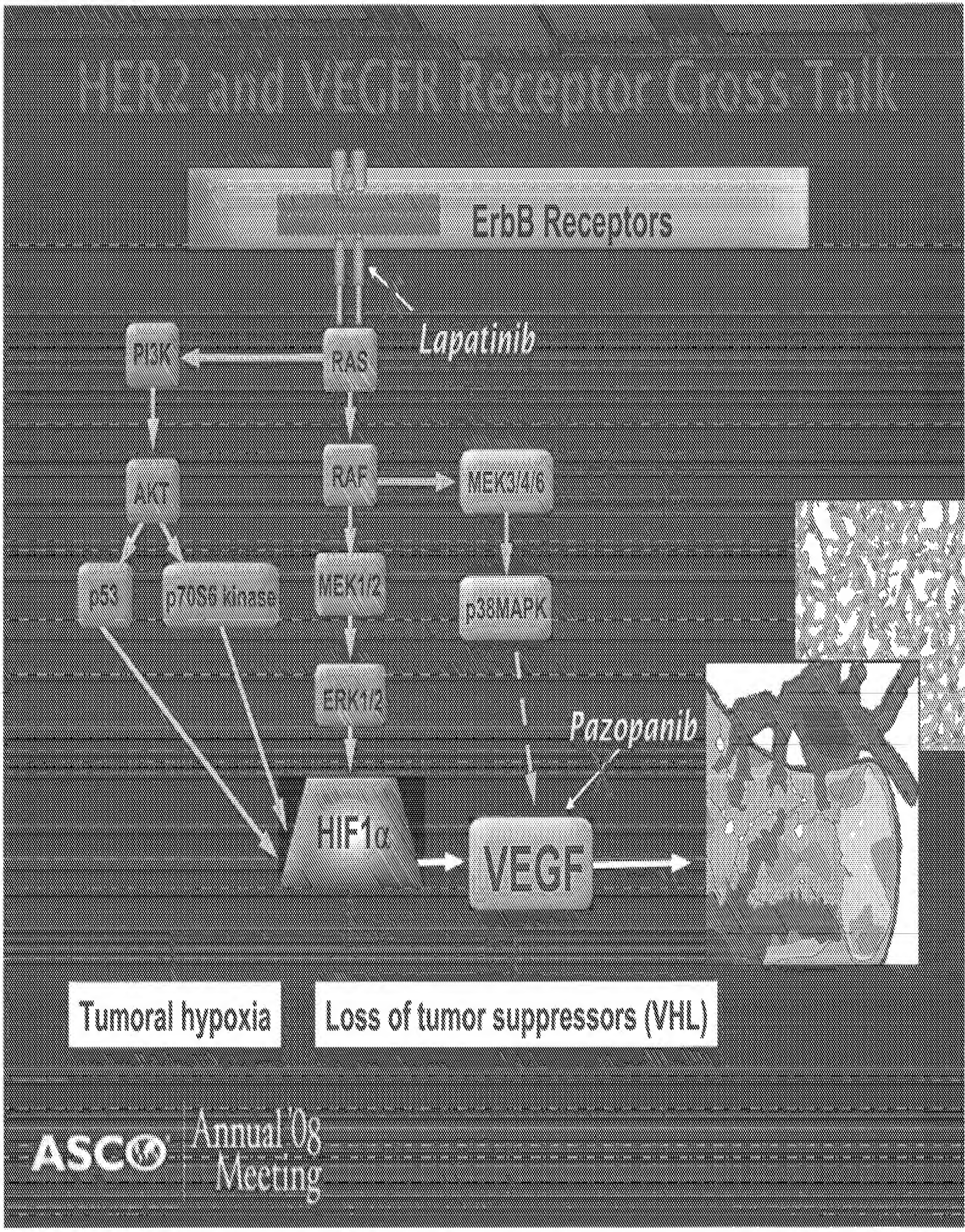
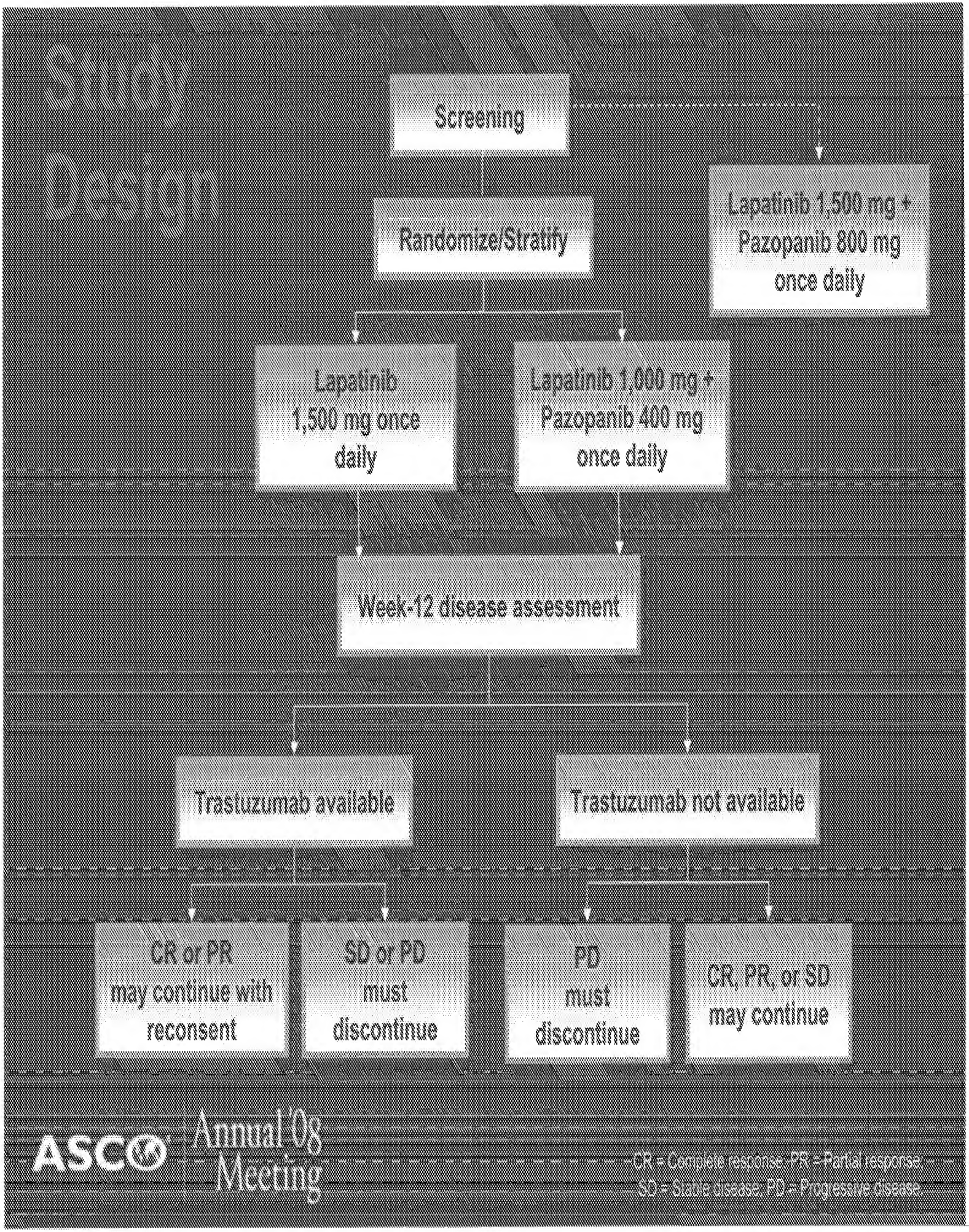
Disclosure Slide

- **Consultant or Advisory Role**
  - Genentech BioOncology
  - GlaxoSmithKline Oncology
- **Honoraria**
  - GlaxoSmithKline Oncology



ASCO Annual '08 Meeting

- To compare the efficacy and safety of pazopanib plus lapatinib versus lapatinib alone in patients with first-line HER2+ advanced or metastatic breast cancer


EGF104900
(EGACT)
Screening
Randomize/Stratify
Lapatinib 1,500 mg + Pazopanib 800 mg once daily
Lapatinib 1,500 mg once daily
Lapatinib 1,000 mg + Pazopanib 400 mg once daily
Week-12 disease assessment
Trastuzumab available
Trastuzumab not available
CR or PR may continue with reconsent
SD or PD must discontinue
PD must discontinue
CR, PR, or SD may continue
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CR = Complete response; PR = Partial response
SD = Stable disease; PD = Progressive disease

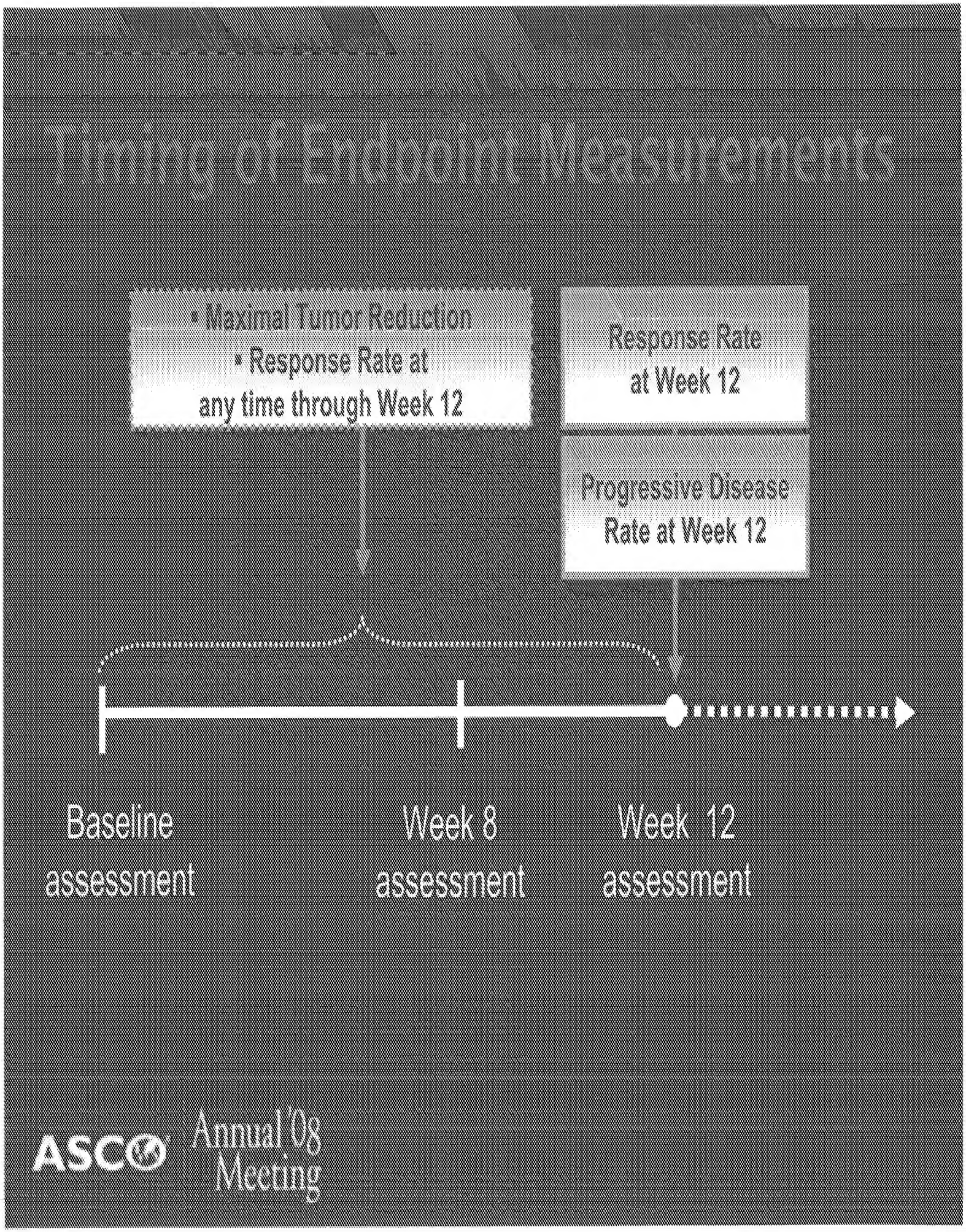
- Inclusion criteria
  - Women ≥ 18 years with stage III/IV invasive breast cancer
  - ECOG PS of 0 or 1
  - No prior chemotherapy or anti-HER2 therapy for metastatic or recurrent disease

- MITT population used for all efficacy analyses
  - All randomized and centrally confirmed HER2 FISH+

MITT = modified intent-to-treat.

Study Endpoints

- Primary endpoint was 12-week progressive disease (PD) rate
  - % with PD 12 weeks after randomization
  - Unknown/missing evaluations counted as PD
- Secondary endpoints
  - 12-week response rate
  - Time to response
  - Response duration
  - Overall survival
  - Safety and tolerability


• Maximal Tumor Reduction
• Response Rate at any time through Week 12
Response Rate at Week 12
Progressive Disease Rate at Week 12
Baseline assessment
Week 8 assessment
Week 12 assessment

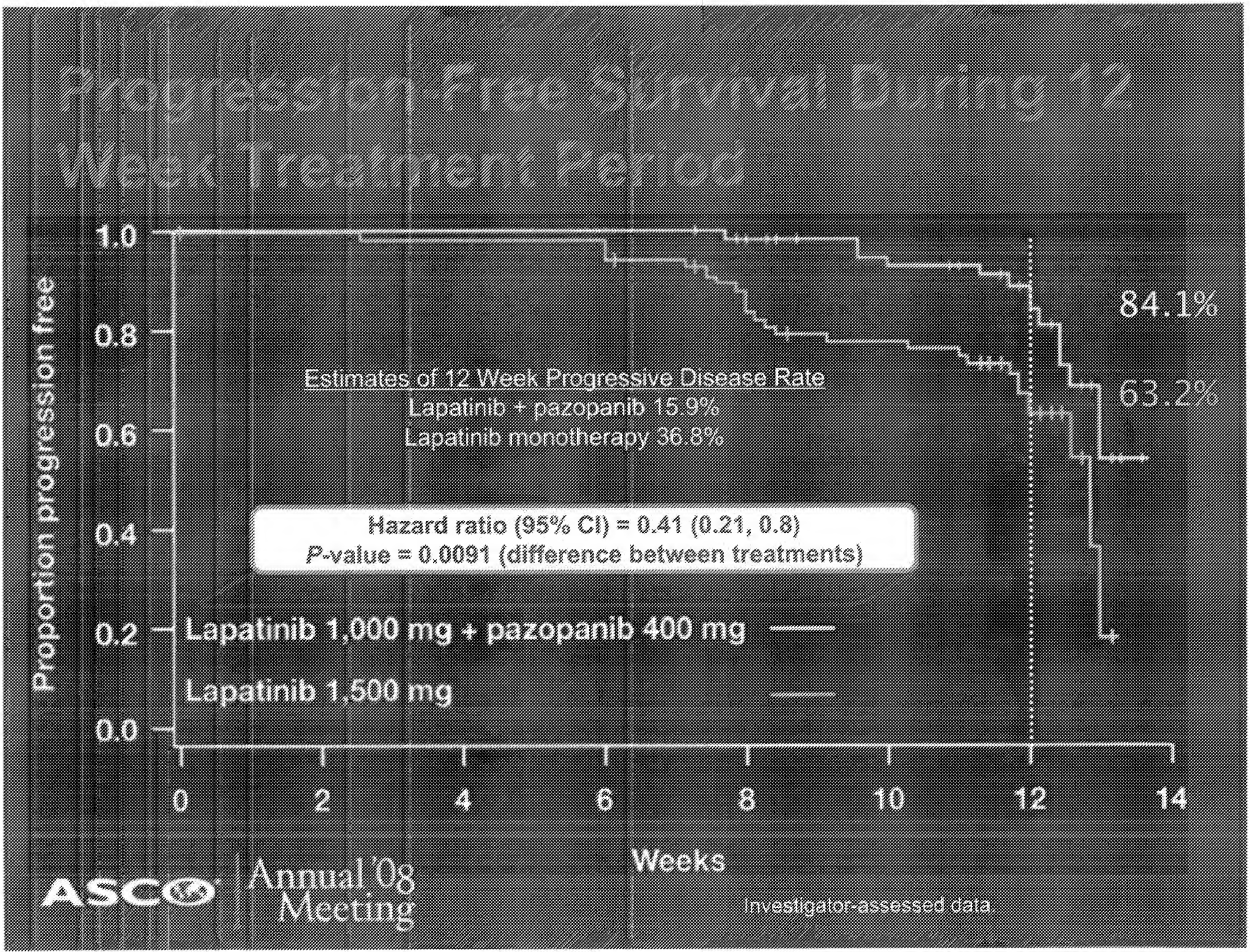
Patient Characteristics

	Lapatinib 1,500 mg (n = 72)	Lapatinib 1,000 mg + pazopanib 400 mg (n = 69)
Mean age, years (SD)	53.5 (11.2)	52.1 (12.8)
Race, n (%)		
Asian	33 (46)	30 (43)
White	19 (26)	18 (26)
Other	20 (28)	21 (30)*
Disease stage at study entry, n (%)		
III	18 (25)	14 (20)
IV	54 (75)	55 (80)
Stratification factors, n (%)		
Visceral disease	41 (57)	37 (54)
ER+ or PgR+	30 (42)	30 (43)
No prior therapy	47 (65)	44 (64)
Median time since initial diagnosis, days	379.5	294

SD = Standard deviation; ER = Estrogen receptor; PgR = Progesterone receptor.

*1 patient in the combination treatment group had missing data.

	Lapatinib 1,500 mg (n = 72)	Lapatinib 1,000 mg + pazopanib 400 mg (n = 69)
PD Rate at week 12, n (%) (90% CI)	28 (38.9) (29.4, 48.3)	25 (36.2) (26.7, 45.8)
	p=0.37	
PD	12 (17)	14 (20)
Unknown	1 (1)	1 (1)
Missing	15 (21)	10 (14)


Proportion progression free
1.0
0.8
0.6
0.4
0.2
0.0
Estimates of 12 Week Progressive Disease Rate
Lapatinib + pazopanib 15.9%
Lapatinib monotherapy 36.8%
Hazard ratio (95% CI) = 0.41 (0.21, 0.8)
P-value = 0.0091 (difference between treatments)
84.1%
63.2%
Lapatinib 1,000 mg + pazopanib 400 mg
Lapatinib 1,500 mg
0
2
4
6
8
10
12
14
Weeks
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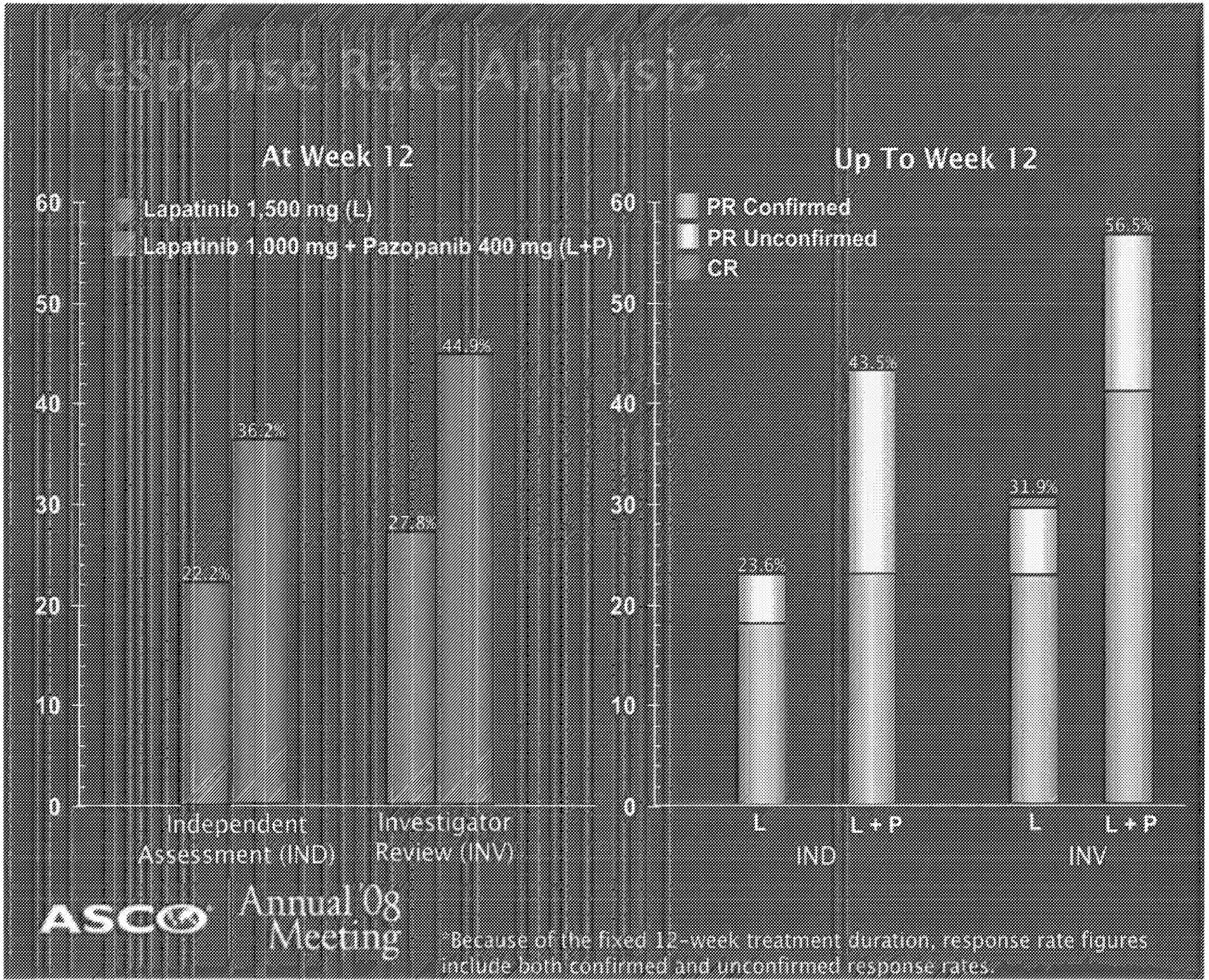
Investigator-assessed data


Response Rates*
At Week 12
Lapatinib 1,500 mg (L)
Lapatinib 1,000 mg + Pazopanib 400 mg (L+P)
60
50
40
30
20
10
0
22.2%
36.2%
27.8%
44.9%
Independent Assessment (IND)
Investigator Review (INV)
Up To Week 12
PR Confirmed
PR Unconfirmed
CR
23.6%
43.5%
31.9%
56.5%
L
L + P
L
L + P
IND
INV
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*Because of the fixed 12-week treatment duration, response rate figures include both confirmed and unconfirmed response rates.

Maximum reduction from baseline target lesion measurement, %
150
100
50
0
−50
−100
−150
Unknown
Complete response
Partial response
Stable disease
Progressive disease
Patients
0 5 10 15 20 25 30 35 40 45 50 55 60 65
Patients
0 5 10 15 20 25 30 35 40 45 50 55 60 65
Wilcoxon rank sum P value = 0.0007 for the difference between treatment groups
Investigator-assessed data
ASCO Annual 08 Meeting

	Lapatinib 1,500 mg (n = 73)		Lapatinib 1,000 mg + pazopanib 400 mg (n = 76)	
Patients, n (%)	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Any event	69 (95)	16 (22)	72 (95)	32 (42)
Diarrhea	42 (58)	4 (5)	51 (67)	7 (9)
AST increase	12 (16)	5 (7)	24 (32)	5 (7)
ALT increase	12 (16)	3 (4)	23 (30)	9 (12)
Nausea	12 (16)	0	22 (29)	1 (1)
Rash	21 (29)	2 (3)	21 (28)	0
Hypertension	3 (4)	0	20 (26)	4 (5)
Vomiting	7 (10)	1 (1)	15 (20)	1 (1)
Anorexia	10 (14)	0	14 (18)	0
Hair color change	0	0	14 (18)	0
Fatigue	7 (10)	0	13 (17)	3 (4)
Dysgeusia	1 (1)	0	12 (16)	0

2 grade 5 adverse events: hepatic failure in monotherapy arm; dyspnea in combination arm

Subclinical LVEF decline

- Asymptomatic LVEF decline ≥ 20% and < LLN (n=3)
- Symptomatic LVEF decline < 20% (n=1)
- All 4 received the combination
- 3/4 subjects had ≥ 1 risk factor(s):
  - Prior anthracyclines (n = 3)
  - Prior radiotherapy to left chest wall (n = 2)
  - History of hypertension (n = 1)
- LVEF resolved/resolving in all 4 patients

Transaminase Elevations

	Lapatinib 1,500 mg (n = 73)		Lapatinib 1,000 mg + pazopanib 400 mg (n = 76)	
Grade, n (%)	ALT	AST	ALT	AST
Grade 1	15 (21)	20 (27)	22 (29)	22 (29)
Grade 2	9 (12)	6 (8)	11 (14)	13 (17)
Grade 3	3 (4)	4 (5)	13 (17)	10 (13)
Grade 4	0	0	0	0
Any grade	27 (37)	30 (41)	46 (61)	35 (46)

Summary

- Increased activity was observed with combination pazopanib + lapatinib when compared to lapatinib monotherapy
  - No difference in PD rate at week 12
  - Response rates were higher in the combination arm compared with the monotherapy arm
  - Almost all patients in the combination arm had a decrease in target lesions
  - Week 12 progression-free survival based on investigator assessment significantly favors the combination arm
- Safety profile of the combination is acceptable
- Confirmation of lapatinib single agent activity in this setting

Conclusions

- First phase II study demonstrating that inhibition of VEGF and HER2 pathways with 2 small molecule tyrosine-kinase inhibitors is effective in first-line HER2+ breast cancer patients
- Further evaluation of this non-chemotherapy containing regimen is planned
- This novel non-chemotherapy based approach represents an exciting potential new paradigm for HER2+ breast cancer patients